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HYPNOSIS AS AN ADJUNCT TO SURGICAL THERAPY

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INTRODUCTION AND HISTORICAL BACKGROUND

HYPNOSIS, from the Greek root "hypnos," meaning sleep, is a term first coined in 1845 by a Scottish physician, James Braid, to describe a state of relaxation which has been self-induced.[2] This condition of self-induced relaxation had been known since Egyptian times, but its use in medicine had its beginning in 1774 with Anton Mesmer.[2, 5] Subsequent workers, such as Liebault, Charcot, and Bernheim, used the hypnotic phenomenon as a psychological tool and clarified the basic reactions of the hypnotic trance so that it could be used as an adjunct to the healing arts.[1, 2]

On April 12, 1829, Jules Cloquet, a French surgeon, for the first time, performed an operation, a mastectomy, on a patient in the hypnotic state.[5] However, hypnoanesthesia and its use in surgery was brought to the fore by James Esdaile,[3] an English physician, who, from 1845 to 1851, performed approximately 300 major operations utilizing this technique. Soon thereafter the charlatan and the stage performer took advantage of the possibilities of hypnosis, and the use of hypnosis in medicine fell into disrepute. The two World Wars produced a tremendous impetus to hypnotherapy, with its particular use in surgical therapy being in the field of hypnoanesthesia.

A report from this clinic was published recently describing the use of post-hypnotic suggestion in the dumping syndrome attending gastric resection for peptic ulcer.[4] The success of this endeavor led us to a continuation of the use of hypnosis in this entity and encouraged us to employ hypnosis in a miscellany of conditions, including lessening of postoperative discomfort, alleviation of bizarre types of pain, and preoperative weight reduction as well as the well-established hypnoanesthesia.

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TREATMENT GROUPS

To date we have treated 105 patients with hypnosis. Of this group, 99 have been followed at least 2 months and are included in this report. They have been divided into five groups.

A. Postgastrectomy Syndrome.—Patients with severe symptoms of dumping following gastric resection have been treated with hypnosis, which is given initially once each week for approximately a month. The intervals between therapy are then prolonged and eventually are discontinued altogether. There have been no dietary restrictions imposed during therapy and, in fact, patients are encouraged to ingest previously offending foods.

B. Postoperative Pain.—In this group, the patient is hypnotized once, or perhaps twice, prior to surgery and given posthypnotic suggestion to ease incisional pain, the discomfort of nasal tubes, urinary catheters, and administration of intravenous fluids, as well as to instill in the patient a spirit of cooperation with the nurses and doctors. All of these patients have had abdominal surgery for benign disease. A control group of patients undergoing similar operations without the benefit of hypnotherapy was observed. All patients were told that narcotics were available, and the nurses on the recovery wards were not informed as to which patients received preoperative therapy.

C. Obesity.—The third group of patients in which we have used hypnosis as a therapeutic tool has been the very obese individual in whom it is axiomatic that postoperative morbidity will be increased. We have attempted to cause a marked weight reduction in these patients without producing the usual discomforts attending dietary restriction. Hypnotherapy in this group has been given at weekly intervals, and it has been found that therapy must be continued for a long period of time in order to reinforce the posthypnotic suggestions.

D. Bizarre Forms of Pain.—In this group of patients are those cases which have unusual types of pain which has failed to respond to the usual conservative measures for relief. Included in this group have been those patients whose pain has come about as the result of surgical therapy, for example, phantom limb syndrome.

E. Hypnoanesthesia.—We have recently begun the use of hypnosis in an attempt to overcome the discomfort associated with minor surgical procedures and particularly endoscopic procedures. In addition to this, with the cooperation of the Anesthesiology Department of this hospital, we have embarked upon a program of hypnosis during the induction of general anesthesia for major surgical procedures.

RESULTS

In these various categories, 99 patients have been treated by hypnotic suggestion (Tables I through IV).

Postgastrectomy Syndrome.—There are 32 postgastrectomy patients who have been treated by hypnotic suggestion; the longest follow-up in any patient is 27 months, with an average of 14 months. Although the evaluation of our

results is difficult because of the subjective nature of this complaint, weight gain is one objective finding which can be utilized. Twenty-six of the 32 patients have gained weight, the average weight gain being 5.4 pounds, with the greatest weight gain 17 pounds. However, 30 patients (94 per cent) have described varying degrees of symptomatic improvement.

An arbitrary evaluation has been set up as follows: a fair result means moderate reduction in severity and/or frequency of symptoms but without weight gain; a good result denotes those patients who have only occasional symptoms, much reduced in severity, and who have gained weight; an excellent result are those patients who are asymptomatic and have gained weight.

TABLE I. RESULTS ACHIEVED IN DUMPING SYNDROME WITH HYPNOTIC SUGGESTION

	NUMBER OF PATIENTS	PER CENT TOTAL
Poor	2	6.2
Fair	6	18.8
Good	12	37.5
Excellent	12	37.5
Patients treated	32	100.0

Pretreatment With Hypnosis for Surgery.—We have given 31 patients, undergoing cholecystectomy, colectomy, and gastrectomy for benign disease, hypnotherapy prior to their procedures. A control group of 31 patients also has been observed. Again, the evaluation of the benefit derived from hypnotherapy is difficult because of its subjective nature. Invariably the treated group indicated that the postoperative period was less difficult than anticipated and a cheerful and cooperative attitude of many of these patients was most encouraging. In addition, interrogation of the nurses and doctors who treated these patients revealed a paucity of complaints when compared with the control group.

One objective method of evaluation is in the amount of narcotics utilized by the patients in both groups. These data are presented in Table II. It can be seen that the average number of doses of narcotics was reduced significantly in the treated group. As an example, in 6 patients undergoing cholecystectomy by the same surgeon, the 4 treated patients received 0, 1, 2, and 4 doses, respectively, whereas 2 control patients were given 8 and 11 doses of the same narcotic.

TABLE II. PRETREATMENT OF PATIENTS UNDERGOING SURGERY FOR TOLERANCE OF PAIN AND DISTRESS OF THE POSTOPERATIVE PERIOD

	HYPNOTIC SUGGESTION GROUP	CONTROL GROUP
Number of patients	31	31
Average number of doses of narcotics	4.2	6.6
Range of number of doses of narcotics	0-9	0-13

Hypnosis for Pain Relief in Bizarre Conditions.—In Table III, the data from 17 patients with unusual types of pain are summarized. The two areas where we have been most heartened by the results have been in those patients

suffering from the phantom limb syndrome and in those unfortunate individuals suffering considerable pain from metastatic cancer. The categories of the results are based on the patients' own evaluations of relief of their presenting complaint and the average period of follow-up is 8.2 months. All patients have been followed to the present time except the cancer group in which follow-up continued until death. The longest follow-up is 17 months in a patient with phantom limb pain.

TABLE III. HYPNOTHERAPY FOR BIZARRE PAINFUL STATES

	NUMBER OF PATIENTS	AVERAGE FOLLOW-UP (MO.)	NUMBER SESSIONS (AVERAGE)	RESULTS			
				POOR	FAIR	GOOD	EXCELLENT
Phantom limb	4	9	3.5	–	–	2	2
Pain with metastatic cancer	3	3.5	5	–	1	2*	–
Arthritis pain	3	5.4	2	1	2	–	–
Facial neuralgia	2	13.5	12	2	–	–	–
Low back pain	2	11	7.5	–	1	–	1†
Bizarre abdominal pain	2	2.5	3.5	–	–	1	1
Postop. bone pain	1	8	6	–	1	–	–
Total	17			3	5	5	4

*One patient had cordotomy 3 months before beginning hypnotherapy.

†This patient had 3 cordotomies by skilled neurosurgeons, the last 2 years before hypnotherapy.

In two instances, pain was relieved by hypnotherapy after failure of cordotomy. One of these is a good result in the cancer group. The other is the excellent result in the back pain group. This patient had had three previous cordotomies at successively higher levels after a laminectomy and spinal fusion. Even the last procedure, a bilateral cervical cordotomy brought only temporary relief; in fact, this patient had been confined to a wheel chair for 2 years prior to hypnotherapy. After only one session of hypnotherapy the patient began to ambulate with a cane and has had no more pain since that time.

Obesity.—Eleven patients, who were previously on various dietary measures without success, were placed on reducing diets reinforced with hypnotic suggestion. As can be seen from Table IV, 6 patients subsequently refused to continue with therapy and were considered failures. The other 5 patients have lost weight as indicated in the table and, most encouragingly, none of these 5 have regained any of the weight they lost.

TABLE IV. EFFICACY OF HYPNOTHERAPY TO AUGMENT WEIGHT REDUCTION IN OBESITY

NUMBER OF PATIENTS	PATIENTS' INITIALS	WEIGHT LOSS (LBS.)	NUMBER OF WEEKS	NUMBER OF SESSIONS	RESULTS
6		Unknown	1-2	8	Poor
5	M. S.	18	16	10	Good
	I. K.	30	16	10	Excellent
	A. C.	13	4	4	Excellent
	H. I.	15	8	6	Excellent
	C. K.	15	52	6	Fair
11 Total					

Hypnoanesthesia.—To date, our experience with hypnoanesthesia has been meager. Eight patients undergoing proctoscopy have been hypnotized prior to the procedure and 7 have experienced no discomfort during the entire endoscopy —in fact, the proctologist said "the sigmoidoscope fell in." One patient received no benefit from hypnosis.

DISCUSSION

When this study was first initiated, we were not certain of the outcome, but we have continued to be very favorably impressed with results in most of the categories under scrutiny. The striking improvement in many of the patients with the postgastrectomy syndrome has been gratifying and suggests that the psychological element must play a substantial role in this condition. It has been reassuring to observe that some of the patients treated earlier have now gone more than a year without any further treatment but with complete freedom of symptoms of the dumping syndrone.

There has been a continuing search on the part of one of us (O. H. W.) over a period of many years for a medium whereby the control of postoperative discomfort could run apace with the achievements in the safety of operative procedures. Ten years ago, Dr. Donald J. Ferguson of this department and Dr. Raymond N. Bieter, Professor of Pharmacology, cooperated over a period of more than a year in the search for a combination of narcotic and sedative agents which would make the recovery phase more tolerable for the patients. No combinations of medications were found superior to Demerol. Little has been accomplished since to enhance the comfort of the postoperative period.

We have been most favorably impressed with the results obtained in pretreating patients before surgical procedures in order to minimize the discomforts of this postoperative period. Not only has the narcotic requirement decreased, but we find almost uniformly a nice spirit of cooperation with the nurses and physicians among these patients.

Some of the results obtained in bizarre types of pain have been nothing less than spectacular. It has been disappointing that some of the patients have found no relief from this form of therapy, but again this may be an indication that there is a deeper psychological problem underlying the presenting complaint of pain.

Obesity probably represents the most difficult group to treat. We feel that this is probably due to the fact that most obese patients have some unexpressed underlying psychological problem which hypnotherapy cannot meet without the additional use of fairly intensive psychotherapy. Although the objective weight loss has in some cases been discouraging, it has been gratifying to find that these patients note that the hunger pains are less, the headaches usually associated with dieting are not present, and they can spurn food more easily.

SUMMARY

It is our feeling that hypnosis is a useful tool as an adjunct to surgery. Its usefulness lies in its ability to allay the fears of the apprehensive preoperative

patient as well as remove the immediate and remote consequences of the surgical procedure itself. It must be emphasized that a willingness as well as ability to cooperate is a sine qua non for the success of hypnotherapy in any subject. It is this very spirit of cooperation once imbued in a patient by the use of hypnosis which enables the surgery to be accomplished in an aura of cheerfulness rather than of resignation. That suggestions can be more easily imparted to patients in the hypnotic than in the waking state is obvious. The experience of this clinic in the management of 99 patients who have undergone hypnotherapy is described.

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INTESTINAL OBSTRUCTION OF THE DISTAL COLON DUE TO MALIGNANCY: SINGLE-STAGE DECOMPRESSION AND RESECTION

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THIS paper deals specifically with malignant lesions of the distal colon which cause acute obstruction and ultimately require a colon resection. Surgical management by means of staged procedures has long been accepted as preferable. This is especially true for the badly neglected patients who come to the attention of the surgeon in a moribund condition. In such instances the mortality and morbidity will be high with any method of treatment. When the patient fortunately comes to surgery during the early phase following complete obstruction it is contended that both decompression and definitive surgery can be done effectively and safely in one stage.

Fluid, electrolyte, and blood deficits are corrected. The admission x-ray of the abdomen will have demonstrated the huge distention of the colon, and the barium enema interpretation usually gives us a diagnosis of the nature of the lesion as well as of its location. Cleansing enemas are now repeated and if they fail to relieve the obstruction urgent surgery is mandatory. In very low lesions it may be possible to pass a catheter with direct vision through a sigmoidoscope and thus relieve the obstruction. When this is not possible operation is done.

METHOD

Based upon the surgeon's decision that he will proceed with operative decompression, bowel evacuation, definitive resection, and primary anastomosis, an adequate abdominal incision is made. The hugely distended transverse colon immediately presents itself. A small area of this bowel is walled off and a No. 16 gauge needle, with the barrel of a 50 c.c. syringe attached, is inserted. Flatus comes through readily and if fluid also comes through it is trapped. If the volume of fluid is large, it is removed by suction from the barrel of the syringe. The bowel collapses satisfactorily and regains some of its thickness. The patient's condition will now be seen to be dramatically improved; his color will be more pink and the pulse fuller. The critical, tense, distention will have been overcome and any danger of accidental perforation removed. Further, and more nearly complete, evacuation of the content of the obstructed bowel remains to be described. The needle is now removed, the puncture closed with a suture, and the area covered with a pad. Safe manipulation and adequate exploration is now carried out. Devitalized bowel and actual perforations are thus not overlooked.

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It is now assumed that exploration has confirmed the diagnosis of cancer as the cause of the obstruction and the lesion is resectable. The small intestines are walled away, tapes are placed to occlude the colon above and below the cancer. These same tapes are tied over a pad covering the lesion to isolate it from further direct contact. The left lateral peritoneal attachments are incised and reflected and the left ureter identified and protected. The retroperitoneal dissection is now continued upward to expose and protect the retroperitoneal portion of the duodenum. In this vicinity the inferior mesenteric vessels or their branches may be identified, secured, and severed.

The normal undistended bowel, well distant to the obstructing cancer, is now severed between occluding clamps. The dissection is again carried cephalad to include the tumor area and its mesentery, stripping everything off the posterior parietes. The extent of bowel that is to be removed is defined by good cancer surgery and the absence or presence of liver metastases. Usually the splenic flexure is taken down, and the entire left mesocolic drainage shed with it, over toward the right where it is proposed to cut through the transverse colon.

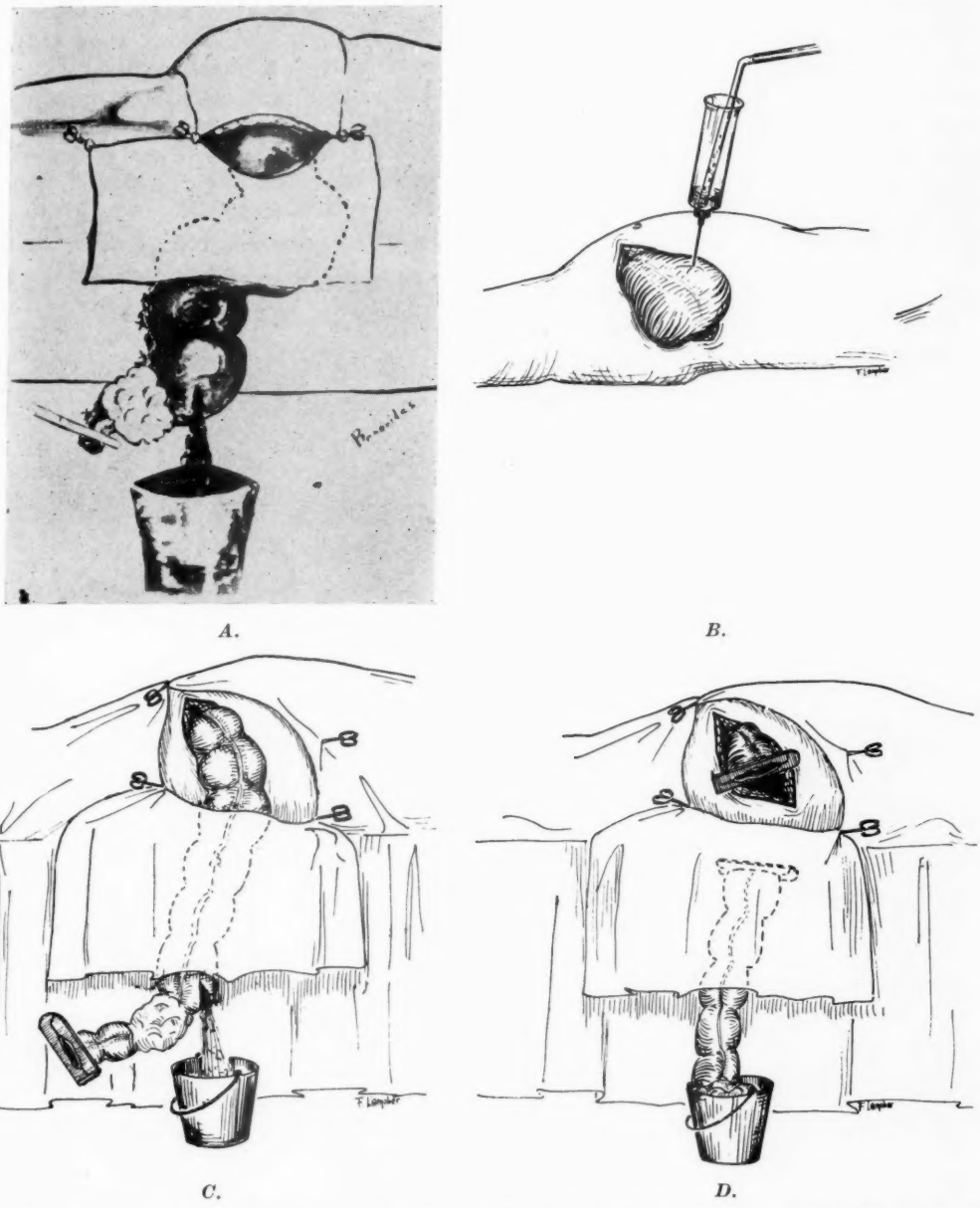
The freed colon, now of substantial length, is eased over the left side of the table to gravitate toward a large pail outside of the sterile field (Fig. 1, *A*). An extra drape is placed over this exteriorized bowel, leaving only a small length centrally to view in the operative field. A circulating nurse now is instructed to make a large opening in the bowel just above the obstructing cancer. Bowel content gushes out into the pail (Fig. 1, *B*). Gentle manipulation and milking of the proximal colon, from the cecum distally, completes the evacuation of nearly all fluid and feces through the exteriorized limb. If necessary, a large caliber Levin tube may be woven up the bowel from below and guided toward the right colon. Through this tube the bowel may be thoroughly irrigated without contamination and a 1 per cent neomycin solution instilled (Fig. 1, *C* and *D*).

The entire colon has thus been rendered quite free of retained fluid, feces, and air. It is collapsed; its walls are substantial for resection and suturing. Return of peristalsis is often noted. Occluding clamps are now placed at the level selected for resection, the area is walled off, and the bowel is severed. The severed limb is allowed to drop out of the clean field as it slips by its own weight beneath the drapes. Adequacy of the blood supply of the retained bowel ends is now ascertained and the anastomosis is made. Just before the anastomosis is completed 1 gram of neomycin in 1 per cent solution is instilled into the bowel through a catheter, the tip directed well above the suture line.

The remaining steps of the operation need not be detailed here. One may have chosen to weave a soft rectal tube up past the anastomosis or be content with sphincter dilation. A complementary tube ileostomy may be necessary, if a significant degree of small intestinal distention is present. Uneventful convalescence is the usual course, and postoperative hospitalization the same as with elective procedures.

CASE REPORTS

CASE 1.—(Miriam Hospital No. 52075.) The patient (J. P.) was admitted Jan. 24, 1955, operated on Jan. 26, 1955, and discharged on Feb. 4, 1955. This 81-year-old woman, on admission, had nausea, vomiting, colic, and abdominal distention of 3 days' duration



A. *B.*

C. *D.*

Fig. 1.—*A*, The exteriorized colon is shown hanging over the left side of the table with a drape excluding it from the operative field. Bowel content is seen gushing out of a rent made above the obstructing cancer, and normal bowel is depicted terminally. *B*, Release of critical distention. *C*, Completing evacuation of bowel and elimination of all distention. *D*, Wide resection completed. Absence of distention allows proceeding with definitive operation indicated by the findings in each case.

which was unrelieved by enemas. There had been a 10-pound weight loss with occasional colic and some diarrhea for at least 9 weeks, although she still appeared well nourished. The abdomen was universally distended, tympanitic, and slightly tender. The vital signs were good though moderate anemia was present. X-rays of the abdomen showed moderate

dilatation of the entire colon and some feces in the cecum, highly suggestive of an incomplete obstruction due to a mass in the rectosigmoid. The sigmoidoscope abutted an obstructing hard annular lesion at 18 cm. which was bleeding actively. A little flatus was seen coming through a probe-sized opening. Repeated enemas gave no results. Her condition worsened (Fig. 2).

An operation was performed 24 hours after admission. A long oblique incision was made on the left side and the large bowel was found extremely distended, more than had been anticipated. The liver and retroperitoneal nodes were found to be not involved. An anterior resection was done with anastomosis of the descending colon to the rectal stump, after decompression and cleansing as described previously. A soft rectal tube was passed anally to a point above the anastomosis. An incidental appendectomy was performed because the appendix appeared inflamed. The operation lasted 2 hours and was well tolerated by the patient. The blood pressure at the beginning had been 150/90, during the course 120/60, and at the termination 140/60 mm. Hg.

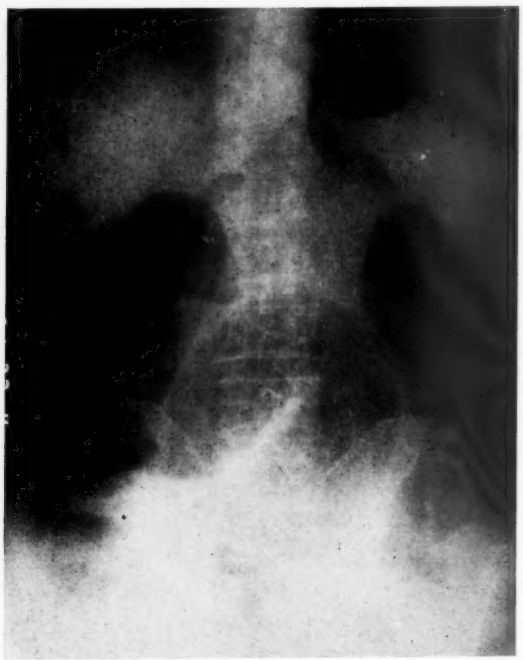


Fig. 2.—J. P., 81, F. Marked distention of entire colon and some feces in cecum due to obstructing cancer at rectosigmoid area.

Pathology: In a 22 cm. length of colon was an annular, hard, constricting lesion 3.5 cm. long, located 5 cm. from the resected end, characterized by central ulceration, infiltrating through mucosa and serosa. Microscopic examination revealed a mucinous secreting adenocarcinoma extending into pericolic fat, metastatic involvement of lymph nodes, and a gangrenous appendix.

Postoperative course: Convalescence was disturbed only by minor gastric retention due to intolerance of hospital food. The temperature never rose above 100° F. for the first 3 days, then was normal. The patient ambulated early, passed flatus by the fourth day, ate well, and had normally functioning bowels by the seventh day. She was discharged on ninth postoperative day, with a primary healing.

Follow-up: The patient did well at home with complete recovery. She was readmitted on Jan. 6, 1956, and died on Jan. 26, 1956, in a coma due to cerebral metastasis. There had been vomiting and weight loss for 6 weeks. The bowels were open and the abdomen flat. X-rays showed the gastrointestinal tract free of ulceration or growth, the genitourinary tract and metastatic series were negative.

Autopsy: Metastatic adenocarcinoma of liver, left ovary, and peritoneum, and hydronephrosis and hydroureter on the left were found at autopsy. The anastomotic scar was intact. Tumor involving the left ovary compressed the left ureter; some of the mass and nodules bulged into the colonic lumen without ulceration of the mucosa. The brain was not examined.

CASE 2.—(R. I. Hospital No. 539976.) The patient was admitted on Feb. 25, 1955, operated upon on March 2, 1955, and discharged on March 12, 1955. This 75-year-old woman (M. S.) had a 4-year history of progressive obstipation with 4 months of virtual starvation. The x-rays on the day before admission showed complete obstruction at the lower sigmoid with huge amount of fecal material in colon. The patient was a severe arthritic and had taken cortisone for the past year and lived on whiskey. She was pale, elderly, emaciated, edentulous and was virtually skin and bones with spindly legs. The abdomen was softly distended with palpable loops filled with gas and feces throughout. Sigmoidoscopy to 11 cm. disclosed a dirty, bloody discharge. Barium by enema would not pass a complete obstruction (Fig. 3).

She was prepared with blood transfusions, neomycin, vitamins, whiskey, and cortisone. Phosphosoda and enemas were useless.

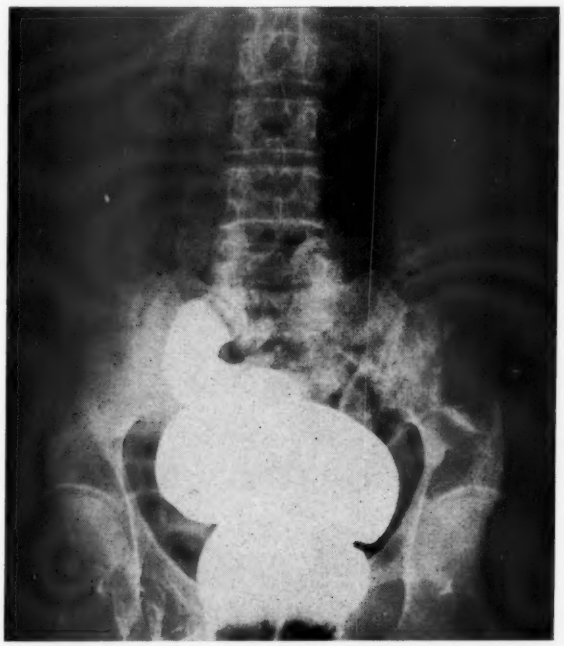


Fig. 3.—M. S., 75, F. Large bowel filled with feces due to obstructing lesion in low sigmoid colon.

Operation: On the fifth day, operation was performed using a long left oblique incision. A completely obstructing lesion was found in the lower sigmoid. Pasty material and flatus distended the entire colon, including the cecum. Exploration, after preliminary decompression, showed no liver, retroperitoneal, serosal metastases. Operative bowel evacuation, flushing, and instillation of neomycin were carried out by my method. A segmental resection was made with an open end-to-end anastomosis of the descending colon to the rectosigmoid junction, with one layer of 4-0 cotton; time 2 hours, 10 minutes. The blood pressure was steady throughout. The patient was in excellent condition with the abdomen flat at the end of surgery.

Pathology: A 29 cm. segment of colon was involved, 9 cm. below and 20 cm. above the lesion. The lesion was a polypoid mass with a 3 cm. base and 5 cm. crown. There was induration of surrounding mucosa and submucosa. Invasion and obstruction of bowel wall with marked inflammation and necrosis was found. Two of 11 lymph nodes contained metastatic cancer.

Postoperative course: The convalescence was uneventful. There was only one temperature elevation of significance on the second postoperative day to 103.2° F., which was unexplained, then it was normal from fourth day to discharge. The pulse was never over 90. The bowels opened on third day, and the patient took feedings beginning the second day. Ambulation was early, closely supervised due to depletion from 4 months' starvation. She was discharged on the tenth postoperative day, with primary healing.

Follow-up: Weight gain was slow, persistent, but substantial. She returned to household duties, but was troubled with arthritis and arteriosclerotic heart disease; however, she continued active. She died suddenly from a coronary heart attack on May 28, 1957. Autopsy was not obtained.

Fig. 4.—M. S., 70, M. Massive distention of small and large intestines with evidence of a low large bowel obstruction in lower descending colon.

CASE 3.—(Miriam Hospital No. 52746.) The patient was admitted on March 7, 1955, operated upon March 8, 1955, and discharged on March 16, 1955. This patient (M. S.) was a 70-year-old man admitted in acute distress after a 24-hour history of obstipation, colic, and vomiting. He appeared gravely ill, the abdomen was hugely distended, firm, tender, tympanitic, with high-pitched sounds. The patient was diabetic and on daily insulin therapy as well as being arthritic and on cortisone which had been discontinued 5 weeks previously due to hematemesis. There was also an x-ray diagnosis of a gastric ulcer.

Para-admission x-rays showed massive distention of small and large intestines (Fig. 4), with evidence of a low, large bowel obstruction. The rectal ampulla was found empty and clean. There was hemoconcentration. Fluid replacement was started at once. Levin tube and enemas gave negative results. Cortisone acetate prophylaxis was used. Surgery was urgent.

Operation: Three and one-half hours after admission, the patient was operated upon. A long left oblique incision was used. There was enormous distention which was deflated through a needle. Exploration revealed the liver, retroperitoneal nodes, and peritoneum to be free of metastases. An annular cancer was found at the lower descending colon which was causing complete obstruction. The sigmoid was fixed in 180 degrees of congenital torsion. The bowel was mobilized and prepared operatively by my method. An end-to-end open anastomosis was made after segmental resection of a greater part of the descending

colon and most of the sigmoid. The length of time of the operation was 3½ hours. The anesthesia record shows a stable course throughout the procedure with the blood pressure maintained at about 155/60 mm. Hg; pulse ranged from 80 at the beginning to 90 toward the middle of the operation, and 68 at the end. When the patient was taken from the operating table, the abdomen was perfectly flat.

Pathology: In a 42 cm. segment of colon, a firm, annular, constricting lesion, 4.5 cm., infiltrates through muscularis and into serosal fat. Microscopic examination revealed adenocarcinoma. The lymph nodes were not involved.

Postoperative course: The convalescence was benign, highest temperature 99.2° F. Healing primary. Ambulated from the first postoperative day. Flatus was passed on third day when oral feeding was started. The diabetes was well controlled and there was no evidence of adrenocortical insufficiency. Just before discharge on the eighth day, x-rays showed the gastric ulcer to be much smaller.

Fig. 5.—F. D., 56, F. Marked distention of large bowel down to midsigmoid and moderate dilatation of small intestine due to obstructing cancer in midsigmoid.

Follow-up: There was complete rehabilitation. The patient had a bilateral inguinal hernia repair on Jan. 6, 1956. He had chronic constipation. Barium enema and gastrointestinal x-rays made on March 13, 1957, were negative. The patient died suddenly during sleep on July 9, 1957. He was presumed to have had an acute coronary occlusion.

CASE 4.—(Miriam Hospital No. 52741.) The patient was admitted on March 7, 1955, operated upon on March 9, 1955, and discharged on March 20, 1955. This patient (F. D.) was a 56-year-old woman with obstructing carcinoma of the midsigmoid. She had had colic for 6 days, stoppage of bowels for 4 days, and bilious vomiting for 2 days. There was no relief from enemas. The patient entered the hospital dehydrated, with scant urination, the abdomen moderately distended, and no audible peristalsis. Levin tube, hydration, and x-ray studies were done on admission. X-ray films showed marked distention of the large bowel down to the midsigmoid with fluid levels (Fig. 5) and moderate dilatation of the small intestine. Carcinoma of midsigmoid colon with radiographic evidence of complete forward obstruction was postulated by the roentgenologist. The patient was given oral neomycin.

Operation: The operation was performed about 14 hours following admission after adequate hydration. A long left oblique incision extending well beyond the midline was made. A hugely distended bowel was deflated. Exploration revealed no distant metastases. My technique was carried out. Resection was made from mid-transverse colon to well beyond the tumor. One layer of 4-0 cotton was used in an open end-to-end anastomosis. The operation was well tolerated over a 4½ hour period. The anesthesia record shows blood pressures 140/70 to 110/68 and 140/80 mm. Hg in the recovery room. The abdomen was perfectly flat at the end of surgery.

Pathology: In a 75 cm. segment of colon, an annular, hard, constricting lesion, 4 cm. long and 14 cm. from distal end, was found. The serosa was indurated, puckered and centrally ulcerated. Microscopy showed infiltration of the muscularis, but no involvement of lymph nodes.

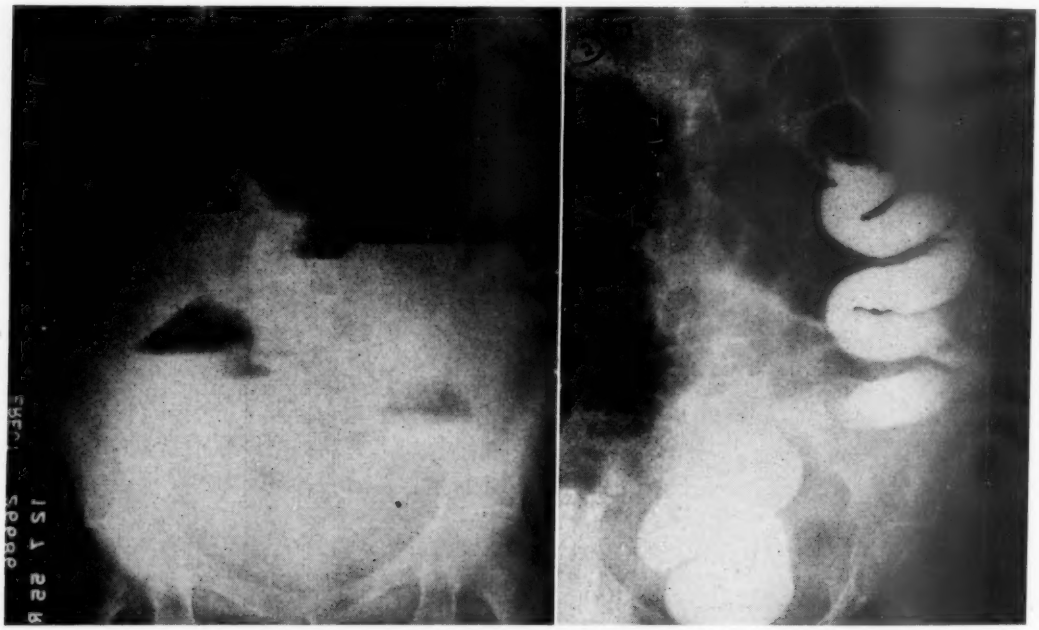


Fig. 6.—G. T., 58, F. Massive distention of small and large intestines due to obstructing cancer in proximal segment of descending colon.

Postoperative course: The convalescence was uneventful; the temperature was never over 100.6° F., and was normal after the fifth day. By the fourth day, the bowels were open and the patient was allowed to ambulate freely. Healing was primary. The patient was discharged on the eleventh postoperative day.

Follow-up: There was full, rapid rehabilitation. Cholecystectomy was performed in May, 1958, at which time no evidence of recurrence was noted.

CASE 5.—(Miriam Hospital No. 56974.) The patient was admitted on Dec. 7, 1955, operated upon Dec. 7, 1955, and discharged on Jan. 1, 1956. This patient (G. T.) was a 58-year-old woman with an obstructing cancer in the proximal third of the descending colon, fixed to the parietal wall. There had been increasing obstipation and vomiting for 3 weeks. X-ray films showed massive distention of the colon proximal to the lesion, as well as distention of the small intestine (Fig. 6). The rectum and descending colon were empty. Enemas gave no return. Her condition worsened gradually. An emergency operation was performed 5½ hours after admission.

Operation: The operation lasted 2½ hours. The blood pressure was extremely labile—140/86 on admission, 190/100 at start of operation, 150/70 first hour, 120/60 second hour, and 96/60 third hour. The pulse varied from 90 at the beginning to 100 at the middle of

the operation and 120 at the end. A long oblique incision was made on the left side extending high up laterally. A large amount of serous fluid was encountered in the peritoneal cavity. The transverse colon was dilated to a diameter of 6 inches and was decompressed through a needle. Exploration noted the lesion below the splenic flexure penetrating and fixed to the parietes. There were no obvious liver metastases. Decompression of the small intestine was done through an ileostomy tube which was left in for postoperative decompression as well. The large bowel was completely evacuated and prepared for resection and anastomosis by the method described. When the splenic flexure was taken down, troublesome venous bleeding in the gastrosplenic omentum occurred. Although the blood pressure fell to 90/60 for a short period, the patient remained warm and free of diaphoresis or other signs of shock. The anesthetist's concern, however, influenced terminating the procedure quickly. The proximal and distal loops were brought out for an obstructive resection, transverse colon to sigmoid colon. The proximal and distal stomas were noted to be of the same size. At end of surgery, the color was good, the blood pressure was 130/60. All finally agreed that she had withstood the surgery very well.

Pathology: In 36 cm. of colon, a 7 by 7.5 cm. foul-smelling, ulcerated, infiltrating, obstructing annular lesion was discovered. Microscopy showed infiltrating adenocarcinoma with invasion of serosal fat and many lymph nodes.

Postoperative course: Convalescence was good. The highest temperature was 100.6° F. on the first day, becoming normal on the sixth through the fourteenth days, at which time a low-grade temperature that lasted to the twenty-seventh day when the colostomy was closed by operation; intra-abdominal excision and end-to-end anastomosis were done. While the splenic area was being inspected, inflammatory exudate was noted at the greater curvature of the stomach. An odorless *Escherichia coli* abscess behind the stomach was uncovered, evacuated, and drained through a separate stab wound. Again, her blood pressure followed an unstable course. Convalescence was uneventful, afebrile throughout, with primary healing. The patient was discharged 11 days later.

Follow-up: The patient was readmitted Feb. 27, 1956, to March 9, 1956, because of metastatic ascites. She re-entered on March 25, 1956, and died 9 hours later following what appeared to be massive embolus of the aortic bifurcation. Autopsy was not obtained.

CASE 6.—(R.I.H. No. 595097.) The patient was admitted on May 12, 1958, operated upon on May 21, 1958, and discharged on June 15, 1958. This patient was a 74-year-old man with carcinoma of the proximal sigmoid which caused incomplete obstruction, anemia, weakness, weight loss, and increasing constipation for more than a year. Blood transfusions and neomycin were administered preoperatively. Catharsis and enemas failed to produce a well-evacuated bowel, safe for resection and anastomosis in one stage.

Operation: On the ninth hospital day, the left colon, from well below the lesion through the distal transverse colon, was taken down, evacuated, and all distention eliminated by my method without soiling. An end-to-end open anastomosis was made; transverse colon to lower sigmoid. The operation lasted 3½ hours. The blood pressure was steady throughout at about 170/80 mm. Hg.

Pathology: In a 48 cm. length of colon, a 4 cm. mass was discovered 8.5 cm. from terminal end. It was an annular, constricting lesion with a fungating luminal mass causing incomplete obstruction. Twenty-nine lymph nodes free of metastasis, but lymph channel invasion seen.

Postoperative course: Ambulation was delayed due to a preoperative injury to the right hip. Thrombophlebitis developed and was treated with anticoagulants. Bowel function returned early; healing was primary. There was a slight temperature elevation for the first 2 days only.

Follow-up: The patient is fully rehabilitated.

CASE 7.—(R. I. Hospital No. 600776.) The patient was admitted on Aug. 26, 1958, operated upon on Sept. 6, 1958, and discharged on Sept. 18, 1958. This patient was an 85-year-old man with carcinoma of the distal sigmoid which caused complete obstruction.

There had been colic, occasional vomiting, and mild diarrhea for one month. Upper gastrointestinal x-rays made 4 days previously; obstruction occurred 2 days prior to admission on August 26. The patient's condition improved rapidly and a repeat gastrointestinal x-ray was done on August 27, showing normal transit of barium. Sigmoidoscopy negative to 24 cm. There was obstruction again and the patient was transferred to the surgical service on August 28. Due to a mix-up in orders, another upper gastrointestinal x-ray examination was made on September 4. The bowel immediately became obstructed, and the patient's abdomen became inordinately distended and the patient gravely ill. Attempts to decompress the intestine again with enemas and long nasal tubes failed in the next 24 hours with condition worsening. Emergency surgery was performed at 4 P.M. on Sept. 6, 1958 (Fig. 7).

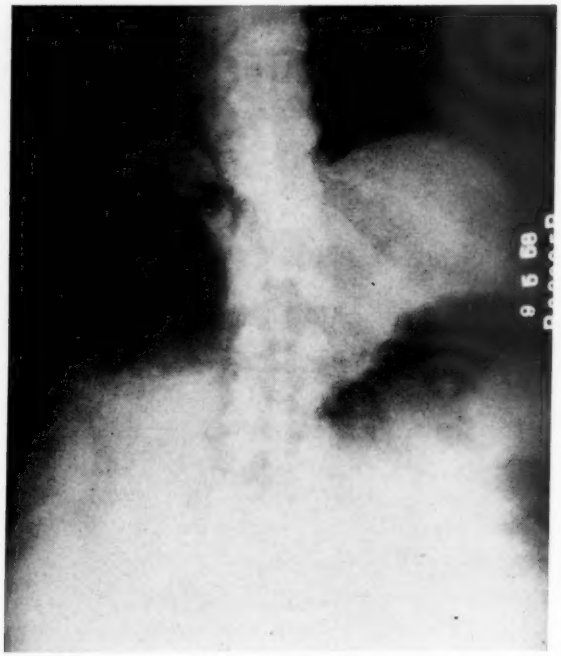


Fig. 7.—T. J., 85, M. Marked dilatation of transverse colon and splenic flexure due to obstructing cancer of low sigmoid.

Operation: The operation lasted 3 hours and was excellently tolerated. The blood pressure ranged during anesthesia from 150/90 first hour, 179/90 second hour, 160/90 third hour, to 150/80 at the end. Cyanosis at the start had disappeared at the end of surgery. While the abdomen was being scrubbed, one standing at the foot of the table could not see the man's head due to the extreme degree of distention (Fig. 8). At the termination of the operation, the abdomen was flat, somewhat scaphoid. My method was employed. A sigmoid resection was done for a constricting lesion which was located 10 cm. above the peritoneal reflection. End-to-end anastomosis between the descending colon and the rectosigmoid junction was effected.

Pathology: In a 25 cm. segment of colon, a 2 cm. annular, constricting lesion was found 8 cm. from the distal end. Adenocarcinoma, with metastasis to 3 of 7 lymph nodes, infiltrates through the serosa into the surrounding fat.

Postoperative course: Fibrillation and retained tracheobronchial secretions, causing atelectasis, disturbed the postoperative course. The abdomen remained soft and flat throughout the convalescence. The temperature was 99° to 100.2° F. for the first 5 days with one spike to 103° F. on the first postoperative day. Healing was primary. The patient ambulated early. He was ready for discharge on the seventh postoperative day, but was held to the twelfth postoperative day for domiciliary reasons.

DISCUSSION

Six of the 7 patients described in this paper and managed by the new method had the highest degree of distention that one is likely to encounter. The ages of the 7 patients were 85, 81, 75, 74, 70, 58, and 56, respectively. These (Table I) were consecutive cases. Operative decompression and evacuation has not been omitted in any patient with obstruction due to cancer of the colon, since this method was initiated. There has been no mortality and morbidity has been low. Each added experience has impressed me and some of my colleagues with the soundness and practical usefulness of the procedure. It is dramatic to see these very ill patients improve on the table as the decompression becomes complete. Their color improves, as does their circulation. This is to be expected, since the physiologic derangement of the bowel has been completely corrected. Peristalsis is often seen in the completely collapsed proximal colon since its caliber and thickness of its walls have returned to normal. Its function to absorb fluids has probably also been restored. At

Fig. 8.—T. J., 85, M. Photograph of hugely distended abdomen just prior to operation.

TABLE I. SUMMARY OF CASE REPORTS SHOWING GENERAL MEDICAL STATUS AND MORBIDITY

PATIENT	AGE	SEX	MEDICAL STATUS	OPERATION	DAYS TO DISCHARGE
J. P.	81	F	Angina, pernicious anemia	Jan. 26, 1955	9
M. S.	75	F	Myocardial infarction, starvation, arthritis	March 2, 1955	10
M. S.	70	M	Diabetes, arthritis, myocardial heart disease	March 8, 1955	8
F. D.	56	F	Healthy	March 9, 1955	11
G. T.	58	F	Healthy	Dec. 7, 1955 Jan. 3, 1956	(11)
T. J.	85	M	Healthy	Sept. 6, 1958	12
C. A.	74	M	Hip injury	May 21, 1958	25

the end of the operation the abdomen is noted to be flat, often scaphoid, and the general condition and appearance greatly improved in comparison to the preoperative status. Marbling of the skin, cyanosis, and thready pulse have been observed to disappear.

Staged procedures for patients with intestinal obstruction leave much to be desired since they introduce their own problems of mortality, morbidity, and expense. Berry[2] records a total mortality of 17 per cent following cecostomy in 115 patients: 6 per cent related to the cecostomy. In an additional 7 per cent, the cecostomy failed to provide adequate decompression. At the Rhode Island Hospital,[10] from 1950 through 1957, there were 175 patients with cancer of the left colon involving the splenic flexure, descending colon, or sigmoid colon. Thirty-one of these had obstructions and were subjected to cecostomy or colostomy with a 13 per cent mortality (Table II). The feeling is generally expressed that staged operations are a small price to pay for the exchange of a live patient. I feel strongly that the patient has a better chance for survival with the new method presented. Since safe and thorough exploration is carried out through an adequate incision, devitalized or perforated bowel demanding immediate attention will not be missed. Mortality and morbidity associated with colostomy, or cecostomy, and ineffective decompression are eliminated. Finally the patient has his cancer operation sooner than is possible with staging, sometimes a matter of many weeks.

TABLE II. MORTALITY IN LARGE BOWEL OBSTRUCTIONS FOLLOWING CECOSTOMY OR COLOSTOMY

AUTHOR	YEAR	CASES	CECOSTOMY	COLOSTOMY
Clement	1953	89	83	24
Gregg	1953	66	11	14
Rankin	1952	16	18	-
Wangensteen	1951	81	-	4
Brindley	1951	46	9	-
R. I. H.	1958	30	17	11
Ulin	1959	167	17	28

Smith, Perry, and Yonehiro[12] studied 1,250 cases of intestinal obstruction. For obstructions of the large intestine they came to the following conclusions: (A) The mortality is related to the degree of distention, as is gangrene and perforation. (B) The very young and the very old tolerate obstruction most poorly. (C) The mortality in infants and children is lower with primary resection than with staged operations. (D) Questionably viable bowel should be resected since the risk of not doing so is far greater. (E) Primary resection can usually be carried out if the degree of distention is not severe. (F) Severe distention contraindicates primary resection. I deny the validity of the last statement; for their own conclusions attest to the fact that it is these severely distended patients in whom thorough exploration and foolproof decompression are almost mandatory. The new method of management presents a way of accomplishing safe, clean, and thorough decompression. The patient is transformed from one who is severely distended to one entirely free of distention. He therefore certainly falls into the group of those in whom the degree of distention is not severe and for whom they conclude that primary resection may be done.

The question has been raised as to whether an adequate cancer operation can be done, under the circumstances presented, by the author's method. The answer is definitely that it can and has been done. This has been demonstrated to my colleagues who have been associated with me during the performance of the operation. The bowel at the time of resection and anastomosis is as well prepared as can usually be accomplished in elective surgery. In the latter, in some instances, after every effort has been made to prepare the large bowel by cathartics and enemas and colonic irrigations, the surgeon is confronted with a bowel still filled with feces or fluid at the time of surgery. This is always frustrating. It need not be and certainly there need be no retreat here to staged procedures. The method described for the patient with an acute obstruction can be utilized here to great advantage and free the surgeon of any frustration. My colleagues and I have utilized the method in such elective surgery with pleasing results (Case 6).

New concepts in bowel surgery have been proposed and accepted after due trial in recent years. At first these new concepts appeared contrary to the well-established practices and seemed to violate sound surgical principles. For acute obstructions of the small intestine, Wangensteen[13] demonstrated the superiority of a one-stage definitive procedure at the time of emergency surgery. Decompression of the small bowel at laparotomy allows visualization of the cause of the obstruction and its management, resection if indicated. The high mortality and morbidity attending staged procedures in these very ill patients, long accepted as inevitable, are now happily relegated to history. More recently for patients with intractable ulcerative colitis, Miller and Ripstein[8] demonstrated the validity of colon resection (partial or complete) at the same time as the ileostomy is made. Here, too, the mortality and morbidity have been drastically reduced compared to that which was obtained when a preliminary ileostomy was deemed a must and a surgical principle not to be violated. The antibiotics have been important in enabling some of the new concepts to be developed; but I believe they play a small part. Improved anesthesia, timely replacement of fluids, and prompt surgery are most important. However, impromptu bowel cleansing and antibiotic sterilization at operation can be accomplished as shown by the work of Poth[9] and by Gliedman and associates.[4] An unreasonably long delay in accomplishing this is not only unnecessary but results in further depletion of the patient's resistance and nutrition. Michel and associates[7] cite transformation from incomplete to complete obstruction in patients undergoing correct preparation for elective surgery. There were 35 such instances in their experience with 11 deaths, a mortality of 31 per cent. In addition, the risk of perforation during attempts at conservative measures should not be underestimated. They advocate exploration through a long incision and feel that better results are obtained if surgery is performed more promptly even when a precise diagnosis cannot be made.

The concept of performing definitive surgery of the colon in the presence of acute obstruction is not new. The experience of other surgeons is interesting and encouraging. Baronofsky[1] cited experience with 2 cases of sigmoid volvulus and one case of sigmoid cancer. Gregg[6] recommends primary

resection in early obstructions when the entire obstructed loop can be removed and when the viability of the bowel is questionable. In 16 such resections, there was no mortality. Smith and associates[11] had three deaths in 37 cases, a mortality of 8.1 per cent. Goligher[5] reviewed experience with 1,644 cases of carcinoma of the colon at Leeds General Hospital and found that 17.6 per cent had obstruction or perforation, or both complications. Of 445 cases involving the splenic flexure, descending colon, and sigmoid, 180 or 40 per cent were cases of obstruction. The mortality was about 34 per cent with all forms of management and in 33 cases of primary resection there were 11 deaths. Ferguson and Chase[3] have been practicing primary resection since 1954. They too stress that adequate management should relieve the distention and remove the toxic content of the bowel as well as relieve the obstruction, permitting a quick return of the intestinal tract to a normal physiologic status. The principle applies to both small and large bowel obstructions. My experience is entirely in accord with this.

SUMMARY

1. A safe, clean, simple method for impromptu decompression and emptying of the acutely obstructed colon, due to cancer of the left side, at the time of emergency surgery is described.

2. Adequate impromptu antibiotic preparation at the same time is carried out.

3. The patient's intestinal tract is rendered free of all distention and emptied of all toxic products, resulting in a patient whose colon has been rendered physiologically normal.

4. Safe, one-stage definitive resection at the same time has been carried out in 6 consecutive patients without mortality and with low morbidity.

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RECONSTRUCTION OF THE PHARYNX AND UPPER ESOPHAGUS

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IN RECENT years, reconstruction of the pharynx and upper part of the esophagus has been required after surgical removal of malignant tumors and occasionally for the relief of benign strictures of these regions.

A few of the cancers of the postcricoid region or upper portion of the esophagus can be resected locally, and the alimentary tube can be reconstructed from the remaining pharyngeal or esophageal wall. Even though the remaining mucosa is extremely limited, pharyngoesophageal continuity usually can be successfully retained by suturing the remaining pharyngeal, upper esophageal, or laryngeal mucosa around a small, nasally placed, gastric feeding tube. Utilization of the pharyngeal mucosa to restore the alimentary canal is the procedure of choice, being used in all laryngectomies and in most cases of partial pharyngectomy for cancer of the pyriform sinus or extrinsic larynx. This type of reconstruction is not the subject of this paper.

Another group of patients have extensive, poorly delineated cancers that may be fixed to the vertebral column or be associated with fixed, inoperable, cervical lymph nodes. These neoplasms are at present incurable by surgical means, and such patients are treated by irradiation. As might be expected, the outlook for these patients is extremely dismal, only an occasional one surviving for 5 years.

In between these two extremes is a group of patients who have tumors that are surgically resectable but in whom resection requires complete removal of a segment of the pharynx or the upper part of the esophagus or both. Reconstruction of the pharyngoesophageal defect is required in such cases, necessitating construction of an alimentary tube from tissue foreign to the pharynx and esophagus. It is this type of pharyngoesophageal reconstruction that is the subject of this paper.

At present, pharyngoesophageal reconstructions may be classified into four major types. The first type is reconstruction of the swallowing tube by means of a free skin graft. The second category involves using local skin flaps from the neck to form a skin-lined tube. This skin from the neck may be a flap designed for pharyngeal reconstruction prior to surgical excision of the malignant tumor, as in the so-called Wookey procedure, or the operation may involve closure of the region about the established pharyngostoma and esophagostoma

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by mobilizing and inverting adjacent lateral skin flaps. This newly formed tube is then covered with skin externally by advancing the skin from the adjacent lateral part of the neck over it. The third method of reconstruction involves use of skin flaps from both the neck and thoracic wall. In these cases, the local skin usually is insufficient or unsatisfactory, so more abundant and better skin is brought to the neck and utilized for the pharyngeal reconstruction. The fourth general method of reconstruction involves use of distant tubes. In some instances, these tubes are lined with skin obtained by inverting the skin from the thoracic wall. These newly made tubes then are left in situ and anastomosed to the pharynx and lower part of the esophagus, or are migrated on a pedicle, with pharyngoesophageal continuity eventually being established. In selected cases, segments of more distal parts of the alimentary tract, such as stomach, jejunum, or colon, are migrated into the thoracic cavity on their vascular pedicle. These tubes can be extended into the cervical region for repair of a defect in the upper part of the esophagus.

During the 10-year period from July, 1948, through June, 1958, a total of 14 pharyngeal reconstructions were completed at the Mayo Clinic. Two of these were of the first type, utilizing a free skin graft to form the lining of the lumen. Eight patients had reconstructions of the second type, in which the pharynx or upper part of the esophagus or both were reconstructed by means of skin flaps from the neck. Six of these eight procedures were reconstructions of the Wookey type, in which the swallowing tube was fashioned from a previously designed cervical flap; in the remaining two procedures in this group, the swallowing tube was constructed by inversion of the local cervical skin about the established pharyngostoma and esophagostoma, the external cover also being provided by skin from the adjacent part of the neck. In 4 patients, the pharynx or the upper part of the esophagus was reconstructed by the third method, namely, the use of skin flaps from the thoracic wall in addition to the local cervical flaps. Reconstructions of the fourth type were not carried out at the clinic during this period.

RECONSTRUCTION WITH A TUBE LINED BY A SPLIT-SKIN GRAFT

In 1950, Negus[7] proposed that the cervical portion of the esophagus be reconstructed by using a polyethylene tube covered with a split-skin graft. This method also has been described by Reidy.[9] The polyethylene stent supporting the skin graft is removed through the mouth 3 or more weeks later. Although pharyngoesophageal continuity can be readily established in one surgical procedure by this method, the formation of postoperative strictures is not uncommon and may even necessitate secondary reconstruction by some other method. Edgerton[4] described a modification of this operation in which a framework of tantalum gauze or stainless steel mesh is used to support the split-skin graft. As already noted, this type of reconstruction was employed at the clinic in 2 patients (Fig. 1).

CASE 1.—A 72-year-old man had noted dysphagia and pain extending to both ears for 10 months. He had lost 8 pounds in 2 months. Appropriate studies revealed a grade 3 squamous-cell carcinoma of the esophagus, just below the introitus.

Resection of the cervical portion of the esophagus and the right lobe of the thyroid by a cervical and sternum-splitting incision was done in August, 1953. The pharyngoesophageal defect was immediately repaired by use of a split-skin graft connecting the pharyngeal and esophageal stumps. This graft was tied over a sponge rubber stent. Although the patient tolerated the immediate surgical procedure well, he died 5 days after operation. Permission for necropsy was not obtained.

CASE 2.—A 67-year-old woman came to the clinic in June, 1955. Biopsy revealed a grade 3 squamous-cell carcinoma of the postericoid region.

Total laryngectomy and partial esophagectomy were done, and the pharyngoesophageal defect was repaired immediately, using a split-skin graft tied over a sponge rubber mold as a stent. The esophageal and pharyngeal mucosa was sutured to the graft. The resected carcinoma was 9.5 cm. in length, extending from the hypopharynx to the esophagus and penetrating the anterior wall of the trachea. Ten days later, the stent was removed via suspension laryngoscopy and a sponge rubber dilator was inserted; this dilator was removed and replaced 2 weeks later.

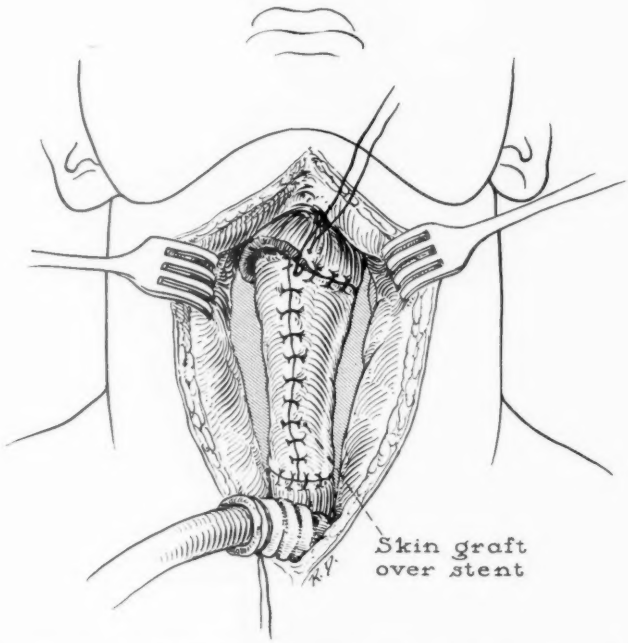

Fig. 1.—Reconstruction of pharynx and upper part of the esophagus by means of a free skin graft over a stent. The upper end of the graft is sutured to the pharyngeal stump and the lower end is sutured to the esophageal stump. The stent (usually a sponge rubber mold) is removed via the mouth 10 to 14 days later.

During the next 5 months, the patient required 15 esophageal dilations. In January, 1956, a recurrent malignant tumor was present in the region of the tracheostoma. This was treated by irradiation with cobalt^{60}. The patient died 1 year after resection of the neoplasm. No statement was available regarding the patient's ability to speak. Swallowing was limited to liquids. The radical excision and reconstruction procedure extended over a period of 7 months, requiring 18 visits to the operating room, and a total of 76 days of hospitalization.

RECONSTRUCTION WITH SKIN FLAPS FROM NECK

Primary Repair With Previously Designed Cervical Skin Flap (Wookey Procedure).—This method is usually employed as a primary procedure after resection of the pharyngoesophageal region, a specially prepared rectangular

cervical skin flap being employed. This type of reconstruction was first employed by Trotter, as described by Pilcher,[8] for re-establishing the pharyngoesophageal continuity after conservative local excision of the pharynx and cervical part of the esophagus. The procedure was further perfected by Wookey,[11, 12] who utilized it after conservative pharyngoesophagectomy with preservation of the larynx and also after radical laryngopharyngoesophagectomy. More recently, this procedure has been combined with unilateral and even bilateral radical dissection of the neck.[2] This type of reconstruction usually provides a swallowing tube which functions well.

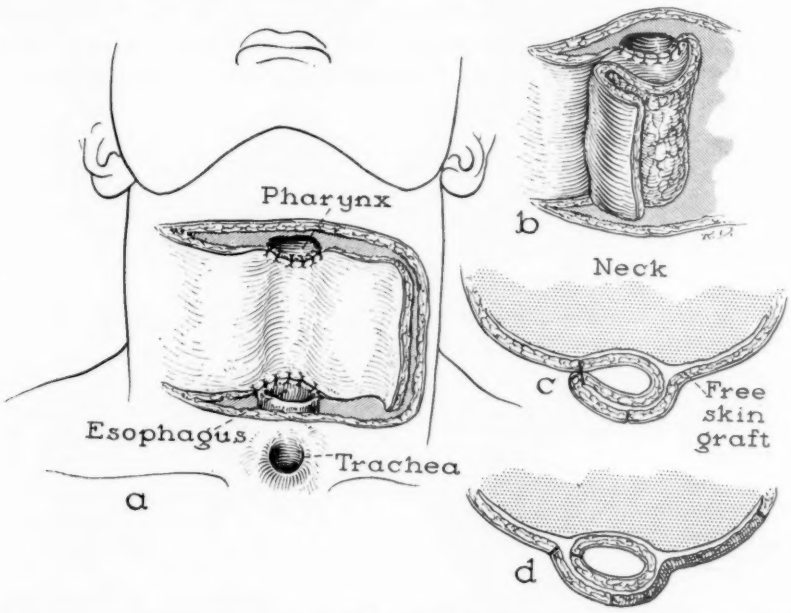

Fig. 2.—Reconstruction of pharynx utilizing previously designed skin flap from the neck (Wookey procedure). *a*, The previously designed flap, with its base on the side of the lesser amount of malignant involvement. The flap is sutured to the posterior portion of the pharyngeal and esophageal stumps. *b*, Flap folded forward and sutured to one lateral and the anterior portion of the pharyngeal and esophageal stumps. This leaves a large open stoma on the side of the base of the flap and a bare area on the opposite side of the neck. This bare area is covered with a split-skin graft. *c*, About 6 weeks later, the lateral pharyngeal stoma is incised longitudinally. This shows the previously placed skin graft in position. *d*, This shows closure of the pharyngeal stoma and completion of the reconstruction.

A rectangular flap is outlined on the neck, with its base on the side of lesser involvement by the tumor or opposite to the side of a proposed concomitant dissection of the cervical nodes. This cervical flap usually measures approximately 12 cm. horizontally and 10 cm. vertically. The flap of skin, including the platysma, is reflected back. Following laryngopharyngoesophagectomy, the flap of cervical skin is sutured to the pharyngeal stump cephalad and to the esophageal stump caudally, the raw surface of the cervical skin flap lying on the vertebral fascia and forming the posterior, one lateral, and the anterior wall of the new pharynx (Fig. 2, *a* and *b*). The reconstructed pharynx is left open laterally, forming a lateral pharyngeal fistula. The remaining area of the neck, devoid of skin coverage, is then covered with a split-skin graft. A nasal gastric feeding tube is placed from the nose and nasopharynx into the newly constructed pharyngeal gutter and into the esophagus and stomach. As an

alternative, the feeding tube may be passed directly into the esophagostoma and into the stomach. The continuous flow of saliva from the pharyngostoma poses a problem in keeping the patient comfortable. In some cases, this has been obviated by temporary suture closure of the pharyngostoma. The patient then is required to rid himself of saliva orally.

At a second stage, 4 to 6 weeks later, the lateral pharyngeal gutter, or sinus, is closed (Fig. 2, *c* and *d*). This is accomplished by undercutting the edges of the sinus and turning the tube of skin inward by sutures with the knots in the pharynx, followed by a second layer of sutures. If the pharyngostoma had been closed previously to prevent salivary dribbling, it is then opened prior to closure of the lateral pharyngeal gutter. Skin from the adjacent part of the neck is then mobilized to provide additional external cover. The nasal gastric tube is left in place for approximately 2 more weeks, at which time swallowing may be started if the wound is completely healed.

As already mentioned, our series included 6 reconstructions utilizing local cervical flaps of the Wookey type.

CASE 3.—A 42-year-old man was treated at the clinic in 1953 by thyrotomy for a grade 2 squamous-cell carcinoma of the left vocal cord. In June, 1955, the patient returned with an obstructing postcricoid carcinoma (recurrent? new?) and a fixed left cervical lymph node. Biopsy of the node revealed grade 3 squamous-cell carcinoma. Roentgen therapy was given to the neck and laryngeal regions, after which a persistent tracheoesophageal fistula developed.

In August, 1955, total laryngectomy, pharyngectomy, and left thyroidectomy were done, and the first stage of a Wookey reconstruction was accomplished by suturing a previously designed cervical skin flap to the pharynx cephalad and to the esophageal stump distally. The bare area in the left side of the neck was covered with a split-skin graft. Examination of the specimen revealed carcinoma, with residual tumor present in the subglottic region and extending into the thyroid gland. In September, 1955, the lateral pharyngeal sinus was closed successfully. The radical surgical excision and subsequent reconstruction required approximately 10 weeks, necessitating 3 operative procedures and a total of 41 days of hospitalization.

Following reconstruction, the patient experienced no difficulty in eating a regular diet and communicated with the aid of a reed type of mechanical voice box. Occasional mild dysphagia was relieved by removal of the growth of hair in the new pharynx. The patient died of widespread distant metastatic tumors 34 months after the reconstruction.

CASE 4.—A 54-year-old woman was seen at the clinic in 1954 for a recurrent (new?) grade 3 squamous-cell carcinoma of the postcricoid region. In 1947, a grade 3 squamous-cell carcinoma had been removed from the postcricoid region by suspension laryngoscopy and electrocoagulation of the lesion. This was followed by roentgen therapy. In 1948, radical dissection of the right side of the neck was done; one anterior cervical node was found to be metastatically involved.

In October, 1954, resection of a portion of the cervical part of the esophagus and the hypopharynx, with preservation of the larynx, was done for the recurrent carcinoma. A previously planned, first-stage Wookey reconstruction also was accomplished. The recurrent tumor measured 8 mm. in diameter. Closure of the pharyngeal stoma was effected in December, 1954. The radical excision and reconstruction were accomplished in 10 weeks, requiring 3 visits to the operating room and a total of 41 days of hospitalization.

Following reconstruction, she could eat a regular diet without difficulty, and she gained 30 pounds. Since the larynx was not removed, speech was not changed. Postoperative esophagoscopy was done periodically. In October, 1957, recurrent grade 3 squamous-

cell carcinoma was discovered at the junction of the normal and the reconstructed portions of the pharynx. This was treated by roentgen rays. In November, 1958, a node containing metastatic tumor was excised from the right auricular region. Recurrence was not present in the pharynx.

CASE 5.—A 53-year-old man came to the clinic in August, 1955, with an extensive, postradiated, grade 3 squamous-cell carcinoma of the pyriform sinus and hypopharynx that extended to the left tonsil. The left vocal cord was fixed, but the cervical nodes apparently were not involved.

Radical dissection of the left side of the neck, total laryngectomy, pharyngectomy, and left thyroidectomy were done, the tissue being amputated through the soft palate and tonsillar region superiorly and through the esophagus inferiorly. The wound was closed with a previously designed Wookey flap, and the remaining defect was covered with a split-skin graft. The resected specimen contained extensive grade 3 squamous-cell carcinoma of the pyriform fossa, extending up through the pharynx into the upper left portion of the thyroid. The cervical nodes were not metastatically involved. In October, 1955, closure of the pharyngeal stoma was effected; a pharyngeal fistula developed that was successfully closed 1 month later. The radical excision and reconstruction were accomplished over a period of approximately 4 months, requiring 3 visits to the operating room, and a total of 37 days of hospitalization.

After operation, he could eat a regular diet. Speech was accomplished by use of a mechanical voice box of the reed type. Recurrent tumor appeared in the region of the tracheal stoma, and the patient died in September, 1956, 13 months after the radical removal.

CASE 6.—A 58-year-old woman came to the clinic in February, 1957. She gave a history of having had a mass in the right side of the neck removed surgically 1 year previously. During convalescence, an abscess developed in the neck, and dysphagia followed. Eight months prior to her coming to the clinic, tracheotomy and gastrostomy had been performed. The patient had lost 35 pounds.

Exploration at the clinic disclosed complete absence of the cervical part of the esophagus and the lower portion of the pharynx. The pharyngeal and upper esophageal defect was repaired by means of a previously designed Wookey flap, and the residual bare area of the neck was covered with a split-skin graft. Six weeks later, the lateral pharyngeal stoma was closed, after which the patient required 3 esophageal dilations. Because these dilations were not completely satisfactory, the reconstructed esophagus was reopened. Stenosis was present at the upper end. The stenotic zone was enlarged and an indwelling plastic-tube obturator was inserted. As a result of this, a small pharyngeal fistula was created in the neck that was closed later. The plastic obturator was kept in place for about 10 weeks and then removed. After one dilation to a diameter of 41 F., the patient swallowed satisfactorily. She has gained 35 pounds. Since the larynx was not removed, speech has remained normal. This reconstruction was accomplished in approximately 6 months, requiring 8 visits to the operating room, and a total of 64 days of hospitalization.

CASE 7.—A 38-year-old woman came to the clinic in January, 1958. Study revealed a grade 3 squamous-cell carcinoma of the postcricoid region extending into the cervical part of the esophagus.

Radical dissection of the left side of the neck, total thyroidectomy and parathyroidectomy, total laryngectomy and pharyngectomy, and partial esophagectomy were done. A first-stage Wookey reconstruction was accomplished, using a previously designed flap. The tumor measured 7.5 by 7 by 1 cm. Two left cervical nodes were metastatically involved. Radical dissection of the right side of the neck was carried out 6 weeks later, and the lateral pharyngeal stoma was closed at the same time.

Since then, the patient has had no evidence of recurrent malignant tumors, but she is receiving Co^{60} therapy to the mediastinal region. Radical resection and reconstruction were accomplished in approximately 10 weeks, requiring 2 visits to the operating room and 48 days of hospitalization. The patient is eating a regular diet and is taking speech lessons.

CASE 8.—A 65-year-old woman came to the clinic in January, 1958, because of intermittent dysphagia for many years that had become worse during the previous month. Appropriate studies revealed a grade 2 squamous-cell carcinoma arising from the posterior wall of the cervical portion of the esophagus.

Laryngectomy, radical dissection of the left side of the neck, left thyroidectomy, and excision of the cervical part of the esophagus were done, and repair of the pharyngoesophageal defect was begun by use of a previously designed Wookey flap. A split-skin graft was utilized to cover the remaining raw area in the left side of the neck. The lateral pharyngeal stoma was closed 6 weeks later, and an acromiopectoral flap was constructed. One month later, this was migrated to cover the defect that previously had been covered by the split-skin graft, which had contracted.

The total excision and reconstruction, including dilations, required approximately 5 months, 6 visits to the operating room, and a total of 35 days of hospitalization. This patient recently died of metastatic mediastinal carcinoma.

Repair by Inversion of Local Cervical Skin Flaps.—In certain instances following partial pharyngectomy or partial cervical esophagectomy, insufficient pharyngeal or esophageal mucosa remains to be sutured about a nasal gastric feeding tube to allow maintenance of pharyngoesophageal continuity. In other instances, pharyngectomy or cervical esophagectomy or both may be required for a patient in whom a Wookey flap had not been previously outlined, and in whom reconstruction using a stent and split-skin graft is not desired. In these cases, the alternative may be to bring out the pharyngeal and esophageal stumps as a pharyngostoma and an esophagostoma, that is, to suture the skin of the lateral aspect of the neck to the posterior border of both the upper pharyngeal and the lower esophageal stumps. After 6 weeks, this surgically produced pharyngeal fistula, or stoma, can be closed by incising and mobilizing the skin immediately lateral, superior, and inferior to the stomas, and inverting the skin to form a skin-lined tube. This same fundamental method is employed in repair of the ordinary variety of pharyngeal and urethral fistulas, and in the construction of the hypospadiac urethra. The skin from the adjacent lateral aspect of the neck is then mobilized and used to give an external covering over the raw surface of the newly formed tube. This general type of closure has been discussed by Conley.[3]

During the 10-year period under consideration, 2 patients underwent reconstruction of the pharynx and upper part of the esophagus by this method at the clinic (Fig. 3).

CASE 9.—A 43-year-old man came to the clinic in September, 1952. Examination revealed an extensive ulcerating grade 2 squamous-cell carcinoma of the larynx, pyriform sinus, and introitus of the esophagus.

Total laryngectomy and removal of a portion of the trachea and a portion of the cervical part of the esophagus and the hypopharynx were done, the esophageal stump being brought out to the skin as an esophagostoma. This left a 7 cm. defect in the hypopharynx and the cervical portion of the esophagus. One month later, the skin about the stomas was mobilized and inverted to form a swallowing tube. Skin from the neck, lateral to this area, was mobilized and brought to cover the newly formed tube externally. This patient received roentgen therapy to the right and left cervical node-bearing regions.

He was living and well in July, 1958, 6 years after operation. He was using an artificial voice box for speech; by masticating his food thoroughly, he has had an excellent

swallowing capacity. The radical excision of the malignant tumor and reconstruction of the hypopharynx and cervical part of the esophagus were accomplished in approximately 6 weeks, requiring 2 visits to the operating room and 45 days of hospitalization.

CASE 10.—A 56-year-old man was treated at the clinic in 1948 for an extensive grade 3 squamous-cell carcinoma of the base of the tongue and valleculae. Treatment consisted of roentgen therapy. In May, 1953, a new (recurrent?) grade 2 squamous-cell carcinoma was noted in the left postcricoid region that extended to the lateral wall of the esophagus.

Total laryngectomy and partial pharyngectomy were done. However, such a narrow strip of pharyngeal mucosa remained that it was impossible to close the pharynx about the nasal gastric feeding tube. Therefore, the pharynx was left open as a stoma, the cervical skin being sutured to the pharyngeal mucosa. One month later, a cervical tube flap was elevated just lateral to the pharyngostoma, and the raw surface under it was covered with a split-skin graft, which was sutured over a sponge rubber stent. After appropriate delaying of the flap, it was turned over and sutured to the opposite side of the pharynx, which resulted in a lateral stoma. One month later, the pedicle of the cervical flap was completely severed and the split-skin graft was removed. The skin from the previously transferred flap was then inverted to close the lateral pharyngostoma, and the suture line was covered with additional skin from the adjacent regions.

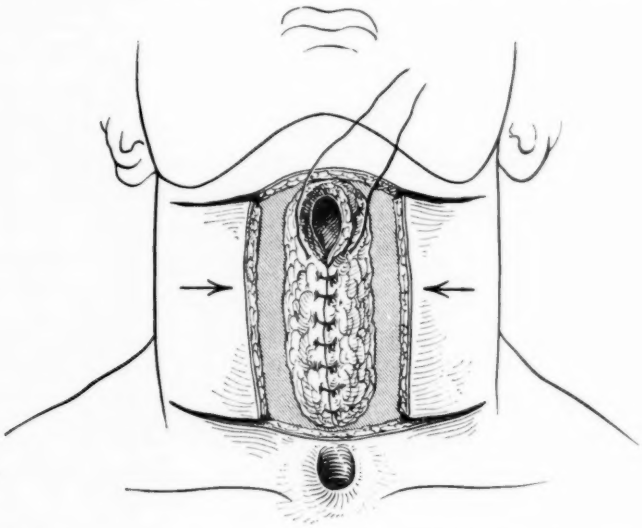

Fig. 3.—Reconstruction of pharynx employing inversion of local cervical skin flaps. The skin about the pharyngostoma and esophagostoma is mobilized and inverted to form a skin-lined tube between the stomas. Lateral cervical skin is mobilized and advanced to provide external cover to the raw surface of the newly formed tube.

The patient ate all food and communicated by means of a voice box. The total excision and reconstruction required 3 months, 5 visits to the operating room, and 30 days of hospitalization.

In June, 1955, recurrence of the malignant tumor was evident in the right side of the neck. The patient died in October, 1955, which was 28 months after radical excision and reconstruction.

RECONSTRUCTION WITH SKIN FLAPS FROM NECK AND THORAX

If the skin on the lateral side of the neck should prove insufficient or unsatisfactory, then the anterior wall of the newly constructed pharynx or the external skin covering or both may be obtained from the upper anterior thoracic wall or the acromioclavicular regions. By means of plastic surgery,

this available skin can be migrated to the midline of the neck. Many different types of closures can be effected by utilization of these methods. Some of these methods of repair have been described recently by Martin[6] and by Lewis[5] and associates.

This type of reconstruction, although usually requiring a somewhat longer period of time, usually results in an eminently well-functioning swallowing tube. Since the skin utilized for reconstruction of a portion of the luminal lining and for the external skin cover is migrated to the neck from some distant regions, such as the anterior thoracic wall or clavicular region, it may be possible in many instances to utilize hairless skin for the reconstruction. This type of skin would be ideal for formation of the luminal lining. In the other types of local cervical-flap inversions in male patients, hair-bearing skin almost certainly will line the newly made pharynx. Dysphagia and partial obstruction from the growth of hair in the pharynx may require removal of the hair. A cervical flap containing hair, although possibly less desirable esthetically, should be used if, by this method, the reconstruction appears simpler, quicker and more certain.

As noted previously, 4 of our 14 patients underwent reconstruction of the upper part of the esophagus or the pharynx by use of flaps from both the neck and thorax (Figs. 4 and 5).

CASE 11.—A 63-year-old man had noted sore throat and pain in the left ear for 3 months. Dysphagia and a 10-pound weight loss were present in the month prior to his registration at the clinic. Examination revealed a grade 2 squamous-cell carcinoma of the left epiglottis and larynx. Laryngectomy was done in June, 1948.

In July, 1952, a new (recurrent?) lesion was found in the hypopharynx. Radical excision of this lesion resulted in a hypopharyngeal defect, the cervical part of the esophagus being brought out as an esophagostoma. Ten days later, two thoracic tubes were constructed bilaterally, with their bases at the clavicular region and the tissue extending caudally. The lower ends of the newly constructed tubes eventually were transferred to the region of the pharyngeal defect, and the skin composing the two tubes was used to reconstruct both the anterior wall of the lumen of the pharynx and its covering skin.

He communicated satisfactorily with a reed type of voice box, and he was able to eat well. The excision and reconstruction were accomplished over a period of 5 months, requiring 8 visits to the operating room, and 39 days of hospitalization. Dilations were not required.

This patient had no further trouble with his pharyngeal carcinoma, but he died in January, 1958. Necropsy revealed primary adenocarcinoma of the stomach.

CASE 12.—A 79-year-old man came to the clinic with a postradiated, recurrent, grade 2 squamous-cell carcinoma of the left epiglottis, vallecula, and pyriform sinus.

In February, 1953, radical dissection of the left side of the neck, total laryngectomy, total pharyngectomy, and partial esophagectomy were done. The neoplasm extended to the base of the tonsil. One left cervical node was metastatically involved. Six weeks later, a Z-plasty was done on the esophagostoma and an acromioclavicular flap was prepared. Two weeks later, or 2 months after the initial radical resection, the pharyngeal lumen was reconstructed by inverting the local skin about the pharyngoesophagostoma, the previously prepared acromioclavicular flap being used to supply cover for the raw surface of the newly constructed swallowing tube. The flap from the acromioclavicular region was selected because of the previous irradiation to the neck.

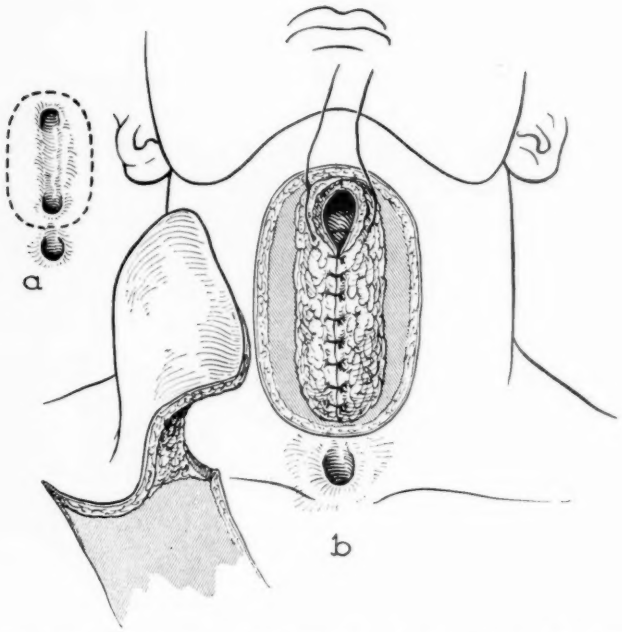

Fig. 4.—Reconstruction of pharynx and upper part of esophagus by employing skin flaps from the neck and thorax. *a*, The local cervical skin about the pharyngostoma and esophagostoma is mobilized and inverted to form a tube. *b*, The external cover to the raw surface of the formed tube is covered with a pedicle flap from the upper thoracic wall.

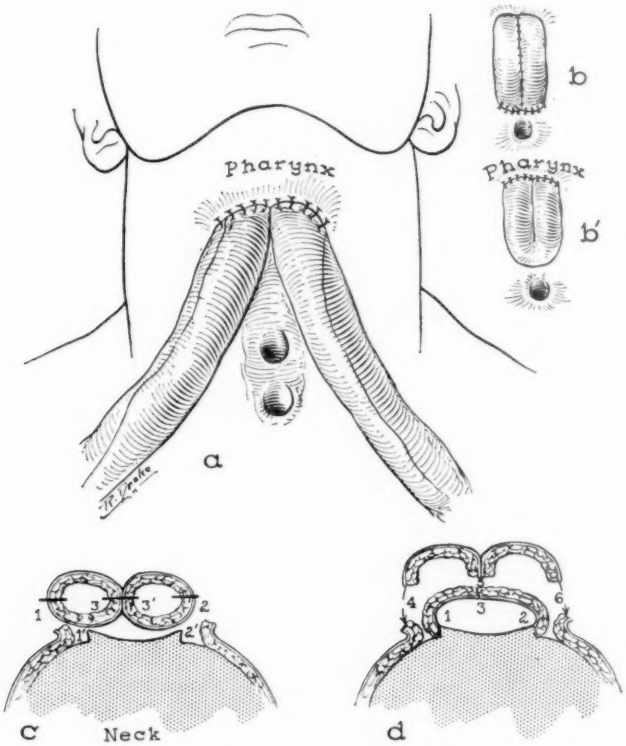

Fig. 5.—Reconstruction of pharynx and upper part of esophagus by employing skin flaps from the neck and thorax. *a*, Large tube pedicle brought from the thorax and attached to the region above the pharyngeal stoma. *b*, Later, the lower end of the tube pedicle is sutured to the region below the esophageal stoma. *b'*, An alternative method employing one tube flap instead of two. *c*, The lateral edges of the tube pedicle are incised longitudinally. *d*, The posterior halves of the tubes are sutured to form the anterior wall of the newly constructed pharynx. The anterior halves of the two tubes are sutured together and also sutured to the lateral neck skin to provide external skin cover for the newly constructed tube.

The patient had satisfactory swallowing and did not require dilations. He communicated with the aid of a reed type of voice box. The radical excision and reconstruction were accomplished over a period of 3 months, requiring 5 visits to the operating room, and 37 days of hospitalization.

This patient died of coronary thrombosis 6 months later. Recurrence of the malignant tumor was not found at necropsy.

CASE 13.—A 40-year-old man had radical dissection of the left side of the neck and total laryngectomy for grade 2 squamous-cell carcinoma of the left pyriform sinus. A 6 by 5 by 4 cm. mass of metastatically involved nodes was present in the resected specimen.

At a recheck examination in July, 1956, a recurrent lesion was noted at the esophageal introitus. A right upper deep-jugular node was clinically involved by metastatic tumor. Radical dissection of the right side of the neck and total pharyngectomy were done. The lateral skin flaps were sutured to the pharyngeal stoma and the esophageal stump was brought out through a stab wound. The excised specimen measured 3.5 by 2.5 cm., and one right upper deep-jugular node was metastatically involved. Two weeks later, a thoracic flap was elevated. This tube flap was delayed and eventually was transferred to close the pharyngeal defect. A tiny fistula developed that closed after minor curettement.

The patient was living and well in April, 1958, almost 2 years after excision of the recurrent tumor. The patient was eating anything, but obstruction of the newly constructed pharynx with hair had occurred once, necessitating removal of the hair. This patient had learned esophageal speech after the initial laryngectomy, but later he used a reed type of mechanical voice box. The radical excision and reconstruction were accomplished over a period of 5 months, requiring 8 visits to the operating room, and a total of 36 days of hospitalization.

CASE 14.—A 52-year-old man came to the clinic in March, 1954, for treatment of an extensive recurrent carcinoma involving the epiglottis, vallecula, right and left vocal cords, and subglottic region. This lesion had been treated first elsewhere 2 years previously by surgical removal of the left vocal cord and roentgen therapy.

At the clinic, total thyroidectomy, total laryngectomy, partial pharyngectomy, and partial esophagectomy were done. The pharyngoesophageal defect was too large to allow primary closure. Therefore, the esophagus was brought out as an esophagostoma, and the cervical skin was sutured about the pharyngostoma. Two months later, a left clavicular tube flap was elevated. After appropriate delaying of the distal end of the flap, it was transferred to the esophagostomal region. Following inversion of the edges of the esophagostoma, the tube flap was used to cover the raw surface over the reconstructed swallowing tube. Two weeks later, the upper pharyngeal stoma was closed by the same technique, and the previously delayed pedicle of the flap was transferred to provide additional cover for the reconstruction. Despite the apparently satisfactory closure obtained, two small pharyngeal fistulas developed. These were closed by simple inversion of the skin edges and closure over them with the adjacent skin.

Excision of the neoplasm and reconstruction of the defect were accomplished over a period of 6 months, requiring 9 visits to the operating room, and 35 days of hospitalization. Since then, 5 esophageal dilations have been required. He was living and well in July, 1958, more than 4 years after the radical excision and reconstruction. He has used an electrolarynx to assist in speech. He has eaten most foods and has gained 35 pounds. Replacement therapy for thyroidal and parathyroidal deficiency has been required.

RECONSTRUCTION BY MEANS OF FOREIGN TUBES

Bricker and Burford[1] recently reviewed the results of their previously described method of constructing a pharyngoesophageal tube by forming it in a manner similar to that of a tubed pedicle flap, except that the cutaneous

side lies inward, lining the lumen, and the subcutaneous tissues lie outward. Such a tube can be used to bridge esophageal defects extending into the mediastinum.

Slaughter and Roeser[10] reviewed the various methods employed in re-establishing pharyngoesophageal continuity by use of mobilized parts from the more distal portions of the alimentary tract. Stomach, colon, and jejunum have been mobilized, brought up, and anastomosed to the upper cut end of the pharynx (Fig. 6). Initially, these mobilized alimentary tubes were tunneled subcutaneously over the thoracic wall and anastomosed in the neck. More recently, the mobilized alimentary tubes are brought through the left hemithorax and through the upper thoracic outlet, being anastomosed to the upper pharyngeal stump. Reconstruction of this type was not employed at the clinic during the period covered by this study.

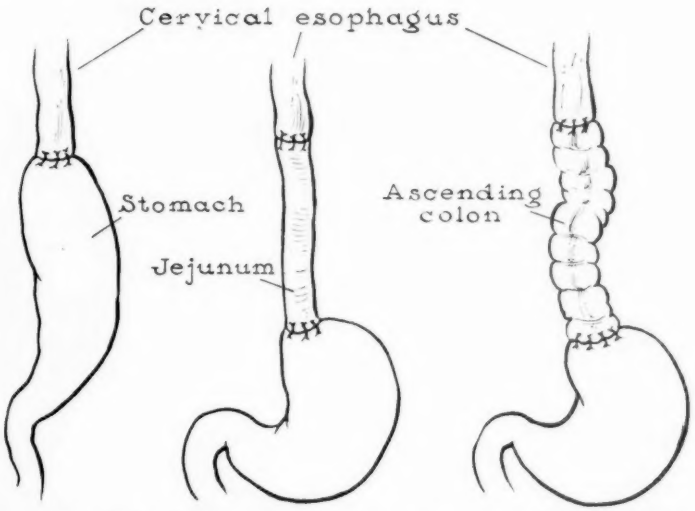

Fig. 6.—Reconstruction of pharynx and upper part of esophagus by means of "foreign" tubes. The stomach may be mobilized and anastomosed to the pharynx or remaining cervical part of the esophagus, traversing the left thoracic cavity. Segments of jejunum or colon may be used to unite the pharynx or the remaining cervical portion of the esophagus to the stomach.

COMMENT

The virtues of surgical treatment versus irradiation for lesions of the extrinsic larynx and postcricoid region will not be discussed. One reconstruction in our series was done for a benign stricture of the upper part of the esophagus, and the patient had a good functional result. The remaining 13 reconstructions were done for defects resulting from radical surgical removal of carcinomas of that region. Although the period required for reconstruction of the pharynx is long and tedious and is an additional financial burden to the patient, the possible increased chance of survival following surgical removal of these selected lesions and the happiness and better nutrition obtained by maintaining the swallowing tube indicate that utilization of these procedures is justified. Although some patients eventually will die of the carcinoma, they will have had a happier and more normal existence with a normally functioning swallowing tube.

Of the 13 patients who had reconstructions after removal of carcinomas, one patient died postoperatively, so that the function of the skin-graft reconstruction could not be ascertained. Of the remaining 12, 5 were living from 6 months to 6 years after reconstruction (6 months, 2 years, 4 years, 4 years, and 6 years, respectively). Two patients died of causes unrelated to the pharyngeal tumor (adenocarcinoma of the stomach in 6 years and coronary thrombosis at 6 months, respectively, after reconstruction). The remaining 5 patients died of spread of their carcinomas. The patient who had a reconstruction by means of the split-skin graft and stent technique required repeated dilations to maintain pharyngoesophageal continuity. In 3 patients, the functional state of their swallowing was not described or it has been too soon after reconstruction to allow adequate evaluation. The remaining patients have had good swallowing, requiring no dilation or only an occasional dilation.

In 2 patients, fistulas developed that did not close spontaneously. Closure was obtained in one patient by curettement of the fistulous tract, whereas the other patient required closure by a local skin flap.

The type of reconstruction employed depends upon the availability of suitable skin for the procedure. If the reconstruction is to be carried out after removal of a heavily irradiated carcinoma, healing may be unsatisfactory following the use of local skin flaps; therefore, distant and healthier skin may have to be brought to the region for the required reconstruction. The use of hair-bearing flaps, although esthetically less desirable, should not be condemned, even though significant obstruction from the accumulated hair in the new pharynx may develop in some patients. However, practically hairless skin usually can be obtained from the region about the clavicles and upper part of the thorax.

CONCLUSIONS

Anyone who undertakes the surgical treatment of carcinoma of the laryngopharynx should be trained in the basic principles of plastic surgery and be conversant with the special problems involved in the reconstruction of the pharynx. There is no "best way" to reconstruct the pharynx, and each patient presents an individual problem that can be solved best by relying on a broad background of basic principles rather than by knowing or depending upon only one method of repair. However, if the tissues of the neck have not been irradiated, if the patient is a woman, and if the size of the defect is not too great, a Wookey-Trotter type of closure is nearly ideal. It is a quick and satisfactory method of reconstruction. Its chief disadvantage is that the flap may slough at its extremity. The method that utilizes a tube of skin requires a much longer time but is practically foolproof and usually can be accomplished for the most part with the patient under local anesthesia. It is ideal for patients who have been irradiated and is somewhat more satisfactory in male patients.

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MAJOR LEG AND THIGH AMPUTATIONS

Ten-Year Survey of Results

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DESPITE many advances in the treatment of peripheral vascular disease, particularly direct arterial surgery, major lower extremity amputations continue to be common operations. There is an increasingly large group of elderly people with a high incidence of peripheral arterial disease challenging us to more informed therapy.

The results of 284 consecutive major lower extremity amputations done at the University of Rochester Medical Center in the 10-year period, 1948 to 1958, are herein discussed in an attempt to learn what changes in management may result in future benefit. Included are all primary as well as secondary leg and thigh amputations done by both resident and attending surgeons. Toe and foot amputations are excluded.

INCIDENCE

In Table I are summarized these lower extremity amputations in regard to age, sex, status, type of anesthesia, whether or not sympathectomy had been previously performed, and whether or not the individual had diabetes. As expected, the majority of these amputations occurred in older individuals. There was a preponderance of men in the series and approximately twice as many ward patients as private patients, although the over-all hospital census does not show a similar predominance of ward patients. Either spinal or general anesthesia was preferred with the occasional use of local anesthesia or of ice in particularly poor-risk patients.

Table I. Statistics on 284 Amputations (237 Patients), 1948-1958 Inclusive

	AGE						SEX	
	<40	41-50	51-60	61-70	71-80	>80	M	F
Calf, 65	2	9	12	27	12	3	45	20
Thigh, 219	5	7	29	63	69	46	132	87

	STATUS		ANESTHESIA				PREVIOUS SYMPATHECTOMY	DIABETES
	PRIVATE	WARD	GENERAL	SPINAL	LOCAL	ICE		
Calf	22	43	21	43	1	0	2	16
Thigh	75	144	56	144	3	16	39	74

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*The contents of this article are the personal views of the author and are not to be construed as statement of official Air Force policy.

The greater number of amputations than patients, of course, reflects the fact that some patients had bilateral amputations or had a calf amputation prior to a thigh amputation. The 219 thigh amputations include a majority of distal femoral supracondylar amputations and a minority of higher ones (including two hip disarticulations). The 65 calf amputations were also studied as major amputations. Indications and results of these lower leg amputations as opposed to thigh amputations have increasingly shown a place for such, since the functional result is better, provided the patient is young enough to benefit from added stump length. Series, such as reported by Edwards and Linton,[2] indicate that excellent results can be obtained if proper case selection is used, but that a certain number still require re-amputation at a higher level due to the failure of healing.

The occasional transmetatarsal amputations done in this hospital are not included herein. The results reported by Warren, Crawford, Hardy, and McKittrick[6] and by Wheelock, McKittrick, and Root[7] indicate that it has a place in management. Many such candidates were handled by single and multiple toe and metatarsal amputations rather than by transmetatarsal amputations here. A significant number of toe or metatarsal amputations were performed on patients in our series prior to the higher amputation, usually on diabetics.

SURGICAL TECHNIQUE

The amputations were performed by various members of the general surgical staff and by a few of the orthopedic staff so that there was some variation of details of technique. The principles of operation which we believe to be of importance are as follows: (1) sufficient skin length in relation to bone length to prevent suture line tension, (2) amputation through noninfected and vascularized tissue with change to a higher level if necessary, (3) avoidance of tissue damage by rough technique, tight sutures, and excess foreign body (including hematoma), (4) brief (48-hour) drainage of the stump to allow escape of collected blood and serum, (5) selection of certain cases for open management rather than immediate closure and prompt conversion to open wounds of any stump that becomes infected, (6) use of a long amputation knife for soft tissues wherever possible to avoid the multiple short cuts of the small scalpel, (7) cutting periosteum at the same level as the bone, (8) simple gut ligation of the nerve without chemical injection, (9) use of wire or synthetic skin sutures to decrease skin inflammation near the suture line, and (10) careful postoperative dressing.

As important as actual technique is the judgment as to timing and site of amputation. Inspection of the tissue at operation may lead to knowledge that an incorrect level has been chosen for amputation and must prompt a change to a more proximal site. Poor healing is not only due to poor tissue but *should be often attributed to poor surgical judgment.*

In summary, it may be said that amputation wounds in the elderly arteriosclerotic individual should receive A-1 surgical technique because of their admitted poor healing characteristics which tend to magnify errors.

ETIOLOGY

As expected, some form of arteriosclerosis accounted for the great majority of indications for both thigh and calf amputations as indicated in Table II. Tissue necrosis, uncontrolled pain, or uncontrolled infection were the usual indications for amputation. The remainder of the operations were scattered between tumor, severe trauma, peripheral embolism, cold injury, and 2 cases of thromboangiitis obliterans. Strict criteria for the diagnosis of Buerger's disease have resulted in a great many patients, previously classified as such, being reclassified as having a form of arteriosclerosis and leaves only the occasional patient with undeniable microscopic evidence of inflammatory disease of the small vessels to fulfill the criteria of thromboangiitis obliterans.

TABLE II. INDICATIONS FOR 284 AMPUTATIONS, 1948-1958 INCLUSIVE

THIGH	NUMBER	CALF	NUMBER
Arteriosclerosis	204	Arteriosclerosis	55
Peripheral embolism	4	Buerger's disease	2
Tumor	6	Frozen foot	2
Trauma	1	Miscellaneous	6
Miscellaneous	4		65
	219		

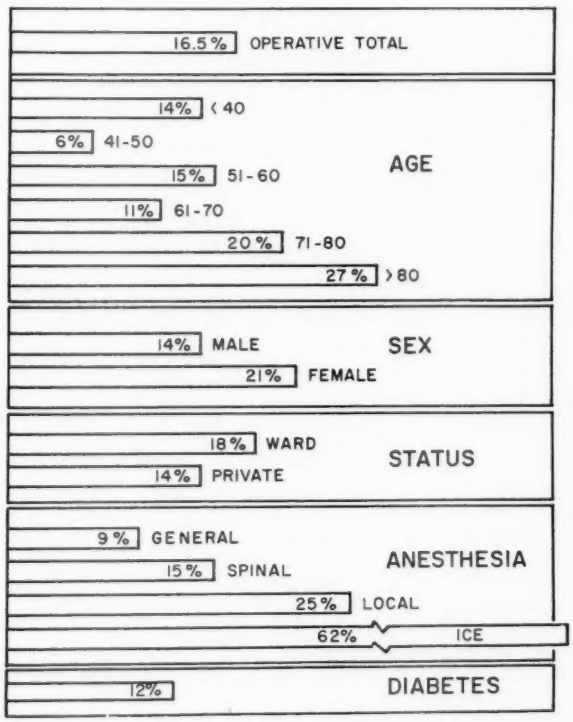

Fig. 1.—Mortality percentages in 1948 to 1958 series of 284 major amputations in 237 patients.

MORTALITY

Table III and Fig. 1 show mortality rates calculated at different decades, indicating the somewhat greater risk to the older patient undergoing amputation. The women in this experience had a 21 per cent over-all mortality while

men only had 14 per cent. The ward patients had a slightly higher death rate than the private patients. When anesthesia was evaluated, it was discovered that general anesthesia was associated with the lowest mortality but this was probably because only good-risk patients were submitted while the poor-risk patients had spinal and the very worst patients had either local or ice anesthesia. The 12 per cent mortality among diabetics was a little less than the over-all mortality by total operations which was 16.5 per cent. (The diabetic patient usually came to amputation at an earlier age than the arteriosclerotic patient.) On the other hand, of the total 237 patients, 20 per cent (or 1 out of 5) died while in the hospital from one cause or another. It would be improper to think that all 47 of these deaths were either the direct or indirect results of the operation itself. It is recognized that by the time an individual has sufficient peripheral atherosclerotic occlusion to cause a degree of tissue necrosis warranting operation that there is probably widespread atherosclerosis occurring in other vital arteries such as the coronary and the cerebral vessels. The 20 per cent mortality does emphasize the danger to the life of a patient occurring when the patient has sufficient disease to necessitate loss of limb.

TABLE III. MORTALITY RATES

	DEATHS/TOTAL	MORTALITY (%)
By age		
< 40	1/7	14
41-50	1/16	6
51-60	6/41	15
61-70	10/90	11
71-80	16/81	20
> 80	13/49	27
By sex		
Male	24/177	14
Female	23/107	21
By status		
ward	33/187	18
private	14/97	14
By anesthesia		
general	7/77	9
spinal	29/187	15
local	1/4	25
ice	10/16	62
Diabetes	11/90	12
Total by operation	47/284	16.5
Total by patient	47/237	20

Various mortality rates are reported by others. Claugus, Graham, Bowling, and Hamilton[1] had a mortality rate of only 6.1 per cent of 82 patients (4.2 per cent of 118 major amputations). Their series from a Veterans' hospital shows a lower rate than most others. Their age group was younger than ours since only 9 per cent of their patients were over 70 while 55 per cent of ours were over 70. Such an age difference indicates a quite different group of patients in that series.

Cause of Death.—The 47 deaths which occurred are summarized briefly in Table IV. It will be seen that some form of heart failure was an extremely

common cause of death since 9 myocardial infarctions are listed as well as 6 other instances of congestive heart failure. Instances of peripheral embolism probably were also secondary to unrecognized myocardial infarction with thrombosis and subsequent embolism from the heart, and some of the instances of pulmonary embolism may have been secondary to this. Pulmonary embolism

TABLE IV. FORTY-NINE* DEATHS AFTER AMPUTATION, 1948-1958 INCLUSIVE

PATIENT	AGE/SEX	P.O. DAYS	CAUSE
			Thigh
H.S. 304392	86/M	5	Myocardial infarction
B.B. 333431	69/F	0	Myocardial infarction and saddle embolism
F.B. 417743	83/F	1	Pulmonary embolism
S.Y. 285168	77/F	5	Pulmonary embolism
E.B. 311111	63/M	7	Bronchopneumonia and saddle embolism
A.B. 56536	85/F	45	Decubitus, infection
I.G. 309175	43/F	0	Cardiac arrest
F.M. 347580	75/M	60	Myocardial infarction
F.B. 276624	66/M	2	? Cause†
M.H. 359393	74/F	7	Aspiration pneumonia
G.H. 311088	60/F	4	Myocardial infarction†
A.P. 93862	79/M	15	Heart failure
G.U. 286497	61/M	2	Pulmonary embolism
F.J. 366985	73/M	17	Septicemia†
L.S. 80801	73/F	14	Cerebral accident
G.L. 102527	79/M	0	Myocardial infarction, pulmonary embolism and aspiration
I.H. 342006	69/F	2	Pulmonary embolism
A.M. 333887	77/F	14	Pulmonary embolism†
A.Y. 352786	92/F	9	Pulmonary embolism
S.P. 328569	90/M	10	Pulmonary embolism†
F.S. 189506	60/M	14	Pulmonary embolism
L.B. 195382	74/F	30	Pulmonary embolism and myocardial infarction
M.E. 365283	70/F	14	Pulmonary embolism†
J.M. 69777	51/M	81	Saddle embolism aorta
H.B. 73364	72/M	11	Mesenteric thrombosis†
S.R. 186563	83/F	75	Bronchopneumonia
A.M. 373696	86/M	1	? Cause
F.M. 314153	64/M		Bowel infarction
L.L. 194423	90/F	7	Pulmonary embolism†
H.C. 42979	75/M	90	? Cause†
H.H. 421690	90/F	6	Heart failure
J.Z. 426830	69/M	17	Saddle embolism
W.Z. 192371	67/M	5	Myocardial infarction
N.B. 438265	60/M	20	Small bowel perforation and peritonitis
C.C. 66503	61/M	0	Heart failure and pneumonia
E.S. 436755	88/M	1	Pulmonary embolism or myocardial infarction
B.S. 449347	78/F	0	Pulmonary embolism
R.F. 446267	55/M	7	Peritonitis after bowel operation
J.V. 119822	64/M	6	Pulmonary embolism
E.R. 427182	81/M	16	Lung abscess and cerebrovascular accident
G.G. 97287	81/F	1	Comatose at operation, carcinomatosis
J.K. 441020	74/F	4	Cerebrovascular accident
I.R. 27558	67/F	28	Peripheral embolization
R.M. 425870	81/F	64	Heart failure and pneumonia
M.W. 435423	80/F	5	Bronchopneumonia
D.B. 321781	85/M	6	Heart failure
			Calf
L.D. 310288	71/M	3	Perforated ulcer and peritonitis
A.S. 339956	66/M	2	Pulmonary embolism†
J.E. 429663	54/M	10	Myocardial infarction

*Two patients in the 1958 group died after calculation of all tables. They are indicated here (to make a total of 49 deaths) but not elsewhere.
†Indicates no autopsy.

occurred 18 times and thus ranks as a major cause of death in the immediate postamputation period. There was also one patient diagnosed as having pulmonary embolism who survived and there were, no doubt, a number of others with minor degrees of pulmonary embolism where the diagnosis was not made.

COMPLICATIONS

Table V indicates the many complications which followed amputation in these patients. Prominent among these was failure of primary wound healing. It is our concept that unless the wound heals per primam without the development of abscess, drainage, or partial opening this should be termed a complication and reference to Table V will indicate that there was a very high incidence of this. A good many of these did not require secondary wound revision but 15 of the 75 so-classed thigh wounds and 21 of the 33 so-classed calf wounds did require secondary operation. Many of the calf wounds required re-amputation at a site above the knee. Other complications are self-explanatory or are discussed elsewhere. Primary wound healing is essential if prolonged hospitalization, often in terms of months, is to be avoided.

TABLE V. COMPLICATIONS IN 284 AMPUTATIONS IN 237 PATIENTS, 1948-1958

COMPLICATION	AMPUTATION SITE			
	219 THIGH		65 CALF	
Failure primary healing	75	34%	33	51%
Wound required revision	15	7%	21	10%
Myocardial infarction	5	2%	1	3%
Cerebral vascular accident	4	2%	0	0
Pulmonary embolism	17	8%	2	6%
Bronchopneumonia	6	3%	0	0
Congestive failure	3	1%	1	3%
Others:				
Mesenteric thrombosis 2, saddle embolism 3, septicemia 1, prostatism 2, peritonitis 2, pneumothorax 1.				

There has been such a high incidence of wound complications following amputation in the elderly arteriosclerotic patient that many surgeons have come to believe that such are unavoidable in a high percentage of cases and are to be explained on the basis of poor vascularity of the tissues and infection present in the lymphatics of many patients. This attitude is not a justifiable one and these wound complications are not to be accepted lightly since a great many of them can probably be prevented by some change in wound management. Although a great many different staff, as well as resident, surgeons performed these procedures, analysis of their individual results shows that some had considerable better success with primary healing than did others. This difference may be due not only to actual technique but to different surgical judgment in determining the proper site of amputation or in altering a procedure already under way and changing it to a higher amputation if the operation under way appeared to be unduly risky in terms of wound healing. This may serve to emphasize an often overlooked point, namely, that personal

statistics on complications and mortality rates do not necessarily reflect those reported by others, although surgeons are prone to think that personal statistics are equivalent to the best reported ones!

Pulmonary Embolism.—Table VI shows 19 instances of pulmonary embolism occurring in the immediate postamputation period. Eighteen of these patients died and one survived. Pulmonary embolism is thus shown to be an important cause of death following amputation. The sources of these emboli were not immediately apparent since they may be secondary to thrombi within the heart as well as within the legs or pelvis. In order to test the hypothesis that a number of these originate from the superficial femoral vein left within the amputated thigh,[5] a series of superficial vein ligations was done at the time of amputation. Although it is recognized in general that this ligation should be done as a bilateral operation (if at all), it was limited to a single side in this series as a clinical experiment. Table VII shows the 27 superficial vein ligations along with complications occurring in those patients. There were the usual group of wound complications and 5 of these patients died. This 19 per cent mortality is approximately the same as the 20 per cent patient mortality for the over-all series. Among these vein-ligated patients, it will be seen that J. V. died of myocardial failure with associated pulmonary embolism, that E. S. died suddenly on the fourth day of suspected pulmonary embolism although there was no postmortem examination, that L. L. was also suspected of pulmonary embolism in the absence of autopsy, and that E. D. apparently suffered a pulmonary embolism. In other words, it is likely that 4 of these 27 patients (15 per cent) had pulmonary embolism despite unilateral superficial femoral vein ligation. Fifteen of the 210 nonligated patients (7 per cent) had pulmonary embolism. The series of 27 vein ligations therefore indicates to us that such is not protective against the development of pulmonary embolization and that it does not appreciably change the over-all risk. Following a study of these results, *simultaneous vein ligation has been abandoned by us.*

TABLE VI. NINETEEN POSTAMPUTATION PULMONARY EMBOLISMS, 1948-1958 INCLUSIVE

PATIENT	AGE/SEX	P. O. DAYS	CAUSE
I.G. 309175	43/F	0	Pulmonary embolism prior to cardiac arrest
M.M. 176429	74/F	10	Survived
M.E. 365283	70/F	14	Sudden, while walking*
A.M. 333887	77/F	14	Sudden, in bed*
L.L. 194423	90/F	7	Sudden (had unilateral vein ligation)
F.B. 417743	83/F	1	Massive
M.G. 282179	80/F	21	Sudden, at home*
G.L. 102527	79/M	0	Multiple
S.P. 328569	90/M	0	Sudden*
G.U. 286497	61/M	2	Multiple
F.S. 189506	60/M	14	Multiple
L.B. 195382	74/F	30	Multiple
A.Y. 352786	92/F	9	Multiple
I.H. 342006	69/F	2	Multiple
S.Y. 285168	77/F	5	Multiple
J.V. 119822	64/M	6	Multiple
E.S. 436755	88/M	4	Sudden (had vein ligation)*
A.S. 339956	66/M	2	Sudden*
B.S. 449347	78/F	0	Sudden*

*Shows no autopsy. All died except M. M.

TABLE VII. SERIES OF 27 SUPERFICIAL FEMORAL VEIN LIGATIONS AT TIME OF AMPUTATION

PATIENT	AGE/SEX	COMPLICATIONS
J.K. 395853	79/M	None
A.T. 283153	74/M	None
I.S. 99798	66/F	None
C.F. 349865	78/M	None
L.G. 412211	83/M	None
M.G. 427285	63/F	None
P.B. 407526	54/M	None
I.W. 427621	77/F	None
H.G. 221701	83/M	None
A.R. 73846	67/F	Wound breakdown
M.S. 354090	82/F	Wound breakdown
C.L. 135787	57/M	Wound breakdown
W.F. 65561	75/M	Wound breakdown
A.T. 424437	53/F	Wound breakdown
H.C. 42979	75/M	Wound breakdown
F.M. 388608	65/M	Wound breakdown
C.D. 159345	89/M	Wound breakdown
E.D. 274500	71/M	? Pulmonary embolism
L.L. 194423	90/F	Pulmonary embolism*
H.H. 421690	90/F	Died, heart failure
D.B. 321781	85/M	Died, heart failure, sixth day
R.M. 425870	81/M	Died, heart failure
J.V. 119822	64/M	Died, heart failure and pulmonary embolism
G.S. 258516	72/M	Slow wound healing
H.Z. 430062	74/F	Decubitus of buttocks
L.S. 375850	86/F	Small flap necrosis
E.S. 436755	88/M	Sudden death, fourth day*

*Shows no autopsy.

DISCUSSION

Analysis of this 10-year experience indicates the serious situation in any patient with advanced arteriosclerosis which requires major leg amputation. The 20 per cent hospital mortality rate of this study was not unexpected since a previous study here[3] had shown that 21 per cent of 33 patients over 60 having amputations in a one-year period died in the hospital. The risk was even greater statistically than it was for people over 60 years of age undergoing a major procedure, such as subtotal gastrectomy (4 per cent of 27 in that series). Arteriosclerosis of a degree necessitating major amputation results in a selected group of patients whose outlook is poor. Advances have, however, resulted in lowered risk since the last reported experience here in 1940 by Pearse and Ziegler.[4]

The incidence of poor wound healing indicates the need for further improvement in wound management. It is believed that a considerable number of these could be prevented by attention to surgical principles which may be neglected during amputations. For example, the stump is a large raw surface which will form serosanguineous exudate, despite the most meticulous hemostasis. Drainage of this for a few days, as is done following radical mastectomy, allows the flaps to adhere quickly to the underlying tissue and prevents pooling of an excellent culture medium in the wound. Removal of the drain can be accomplished without dressing change (and its consequent disturbance of the healing flaps) by leading the drain out one corner of the dressing and burying its end superficially in the dressing.

Tight flap closure is often seen and is due to short flaps with a long bone end. Hope that such will heal often leads to wound complications which could be avoided by further bone resection at once. There should be no hesitation in taking another inch of bone if the wound is too tight, because failure to do so at the time often leads to prolonged hospitalization and the necessity for wound revision. Rough handling of the flap edges may lead to localized necrosis and subsequent wound infection.

Other technical and judgment errors are common. However, their present incidence should not serve as indication that high wound complication rates are inevitable but should spur efforts to improve the situation.

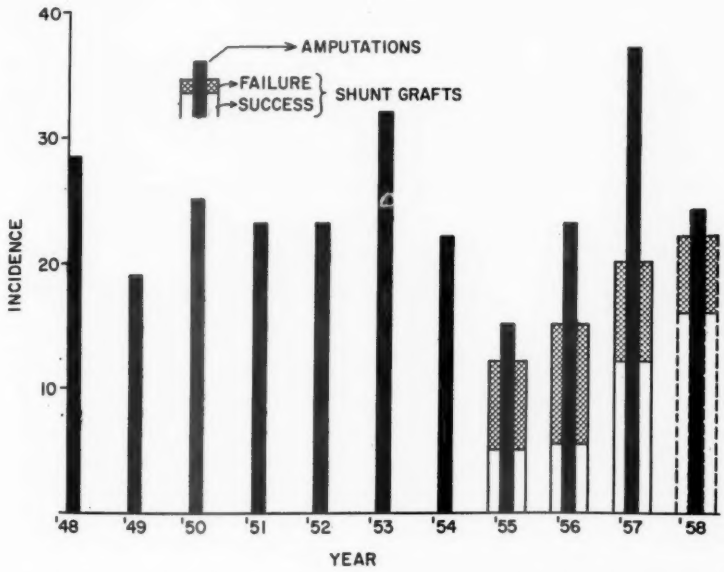

Fig. 2.—Comparison of yearly amputation rate and of yearly arterial shunt grafting incidence and success in the 1948 to 1958 series. The shaded portion of the shunt graft bar indicates failure while the open portion indicates success at the time of latest examination of the individual. The 1958 results do not include the entire year and therefore are indicated as an incomplete series.

In recent years there has been an increasing incidence of direct arterial surgery in the form of vascular shunt grafting, endarterectomy, and embolectomy. The usual operation here has been bypass shunt grafting. In an effort to determine the effect of this upon the over-all incidence of amputation, Fig. 2 was plotted to show the yearly incidence of leg amputations. Superimposed upon the years 1955 through 1958 is the incidence of shunt grafting to bypass femoropopliteal atherosclerotic blocks. Shading indicates successful (at last follow-up) as well as occluded grafts. Although the yearly graft rate has steadily risen, there appears no particular decrease in amputation rate. This probably reflects the use of grafts for disease not threatening early amputation. Too little time has elapsed to learn what the eventual place of such direct arterial surgery will be. Not only must these operations be evaluated in terms of amputation prevention but also in terms of relief of symptoms. Fig. 2 offers one approach to study of the large problem.

SUMMARY AND CONCLUSIONS

The results of 284 consecutive major lower extremity amputations during the 10-year period, 1948 to 1958, are presented with emphasis upon the results in terms of morbidity and mortality. Most of these amputations were due to atherosclerotic peripheral arterial occlusion. The over-all patient mortality rate of 20 per cent emphasizes the danger when a patient has sufficient arteriosclerosis to result in a major amputation. Heart disease and pulmonary embolism were major causes of postoperative death. Unilateral superficial femoral vein ligation at the time of amputation did not lower the postoperative embolism risk or mortality rate and has therefore been abandoned. The high incidence of failure of primary wound healing is related to errors in surgical judgment as well as to errors in surgical technique. Emphasis must be placed upon both to secure prompt wound healing. No conclusion can yet be reached concerning the effect of direct arterial surgery toward lowering the instance of amputation in this hospital population.

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INTRACECAL PRESSURE STUDIES IN THE DOG

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INTRODUCTION

PURGATION has been considered undesirable in acute appendicitis since Fitz's description of the disease in 1886, and a number of statistical studies have shown the harmful effects of such management. Castor oil administration to dogs with experimental appendicitis has also been shown to result in an increased mortality rate. Nevertheless, a surprisingly large number of patients still receive cathartics or enemas after the onset of symptoms, sometimes even upon the advice of attending physicians.[1-3, 5, 8-11]

The first parts of this study were undertaken to evaluate the magnitude and pattern of pressure changes in the cecum following administration of enemas or cathartics and during periods of increased intra-abdominal tension. The final part deals with changes in tensile strength of the healing appendiceal stump. These were thought to be of interest, although problems related to enemas or cathartics are encountered infrequently in post appendectomy patients.

METHOD

Mongrel dogs weighing 13 to 40 pounds were anesthetized with intravenous Nembutal, 30 mg. per kilogram of body weight, supplemented as necessary. Midline abdominal incisions were made with sterile technique. Penicillin and streptomycin were given for 3 days postoperatively, and regular feedings were begun on the second postoperative day.

Intracecal Pressure Following Enemas.—Intracecal pressure patterns were obtained by introducing a balloon attached to a polyethylene catheter into the cecum through the appendix and connecting the catheter to a tambour recording on a kymograph. Numerical values of pressure changes were determined directly with an intraluminal catheter and spinal manometer. Enemas were administered through an inflatable cuff type rectal tube, the final level being adjusted 20, 40, and 80 cm. above the center of the anal orifice. A competent ileocecal valve was simulated by means of a tape passed around the terminal ileum and brought out through the incision after passing through a length of tubing. The terminal ileum could then be opened or occluded with the abdominal incision closed. A simulated Valsalva maneuver was performed on each animal after administration of the enema by application of maximal bimanual pressure to the abdomen.

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Intracecal Pressure Changes With Cathartics.—Three different cathartics were evaluated, each in large dosage, and were administered by duodenostomy tube. Castor oil (2 ounces) was chosen, as it is one of the most commonly used cathartics, although its major site of action is the small intestine.[6] Senna (3 ounces), with primary action on the large intestine, and croton oil (1 ml.), the most drastic known cathartic, were selected for comparison.[6]

Intracecal pressures were recorded continuously by means of a balloon-catheter system connected to a kymograph and to a water manometer. Anesthesia was employed after it became evident in the first 5 castor oil experiments that straining and other motion of the unanesthetized animal interfered with evaluation of pressure changes. Control tracings for periods of 1 to 3 hours were taken prior to injection of the cathartic. Following injection, tracings were taken for 6 to 8 hours, or until an effect was obtained as evidenced by marked pressure changes, hypermotility, or a bowel movement.

Tensile Strength of the Healing Appendiceal Stump.—Appendectomies were performed by doubly ligating the base of the appendix with 2-0 cotton sutures and amputating 1 cm. from the point of ligature. The open stump was cauterized with phenol and alcohol. The stump was additionally inverted with a purse-string suture of 2-0 cotton in 4 experiments each on postoperative days 3, 4, and 5. Bursting pressures were determined on postoperative days 1 through 8, by means of a sphygmomanometer bulb attached to a pressure gauge. In each instance, the abdomen was widely opened so that in situ determinations, not necessitating division of pericecal adhesions, could be performed. After completion of the experiment, the site of rupture was ascertained. Bursting pressures of the normal dog cecum were obtained in fresh postmortem specimens.

RESULTS

A. *Intracecal Pressure Following Enemas.*—Intracecal pressure in 3 animals rose immediately upon administration of the enema, remained at peak levels while the enema was retained, and dropped immediately upon release of the enema. A secondary lower pressure peak occurred immediately after release, and this was followed by a period of cecal hypermotility (Fig. 1).

Direct measurement of intracecal pressure by the water manometer in 6 animals showed pressure to be directly proportional to the height of the enema. Initial intraluminal pressure was found to average 9.5 cm. H_2O. Intraluminal pressure averages of 17.1, 36.2, and 73.2 cm. H_2O were recorded with enema heights 20, 40, and 80 cm., respectively. Final intracecal pressures were identical in the presence of open or closed terminal ileum, although more fluid was required in the former. The small discrepancy between the actual height of the enema and the measured intracecal pressure can be ascribed to the difference in height between the anal orifice and the cecum and the difficulty in determining the exact distance of the cecum from the abdominal wall.

Pressure measurements with simultaneous enemas and simulated Valsalva maneuver showed that an additive intracecal pressure effect occurred (Fig. 2).

B. *Intracecal Pressure Following Cathartics.*—Intracecal pressure during the control periods prior to injection of the cathartics ranged from 6 to 25 cm. H_2O. Following castor oil injection, pressure ranges of 6 to 26 cm. H_2O were recorded. There was no statistical difference between intracecal pressure elevation due to the intraluminal balloon in the control periods and that following castor oil in 5 anesthetized and 5 unanesthetized animals.

Senna administration was followed by a definite increase in intracecal pressure in 2 of the 4 animals, maximal pressures being 33 and 36 cm. H_2O, with a range of 4 to 36.

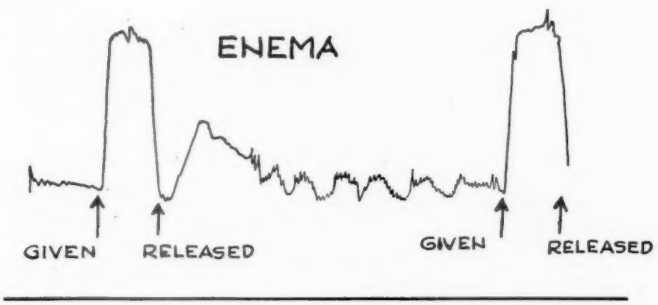

Fig. 1.—Drawing of a kymograph tracing showing the intracecal pressure response to 80 cm. enemas. Immediate rise occurred with administration, immediate fall with release. A secondary pressure peak and subsequent hypermotility were observed.

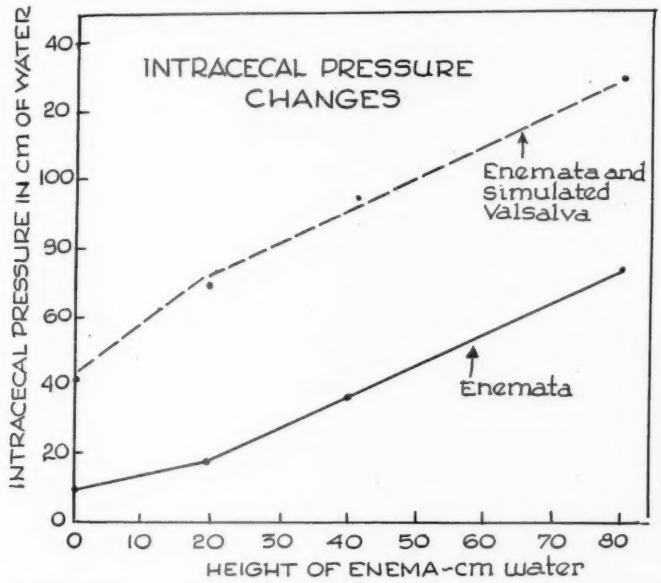

Fig. 2.—Intracecal pressure response to enemas. The pressure elevation was proportional to the height of the enema. An additive effect resulted from a simultaneous Valsalva maneuver.

Croton oil also was followed by an increase in intracecal pressure to 33 cm. H_2O, range 6 to 33, in one of 2 experiments.

Hypermotility of the cecum, following castor oil administration, was noted in 9 of the 10 experiments, appearing from 20 minutes to 4½ hours after administration. The maximum intracecal pressure value was usually associated

with this increase in cecal motility. Hypermotility occurred in one of the 2 animals receiving croton oil and was not observed in the 4 experiments using senna (Fig. 3).

C. *Intracecal Pressure With Straining (Spontaneous Valsalva).*—Several unanesthetized animals exhibited marked straining both before and after cathartic administration. Pressure values possibly obscured by such straining were excluded from the afore-mentioned results. However, it is of interest that intracecal pressure elevations up to 68 cm. H_2O were recorded during these episodes.

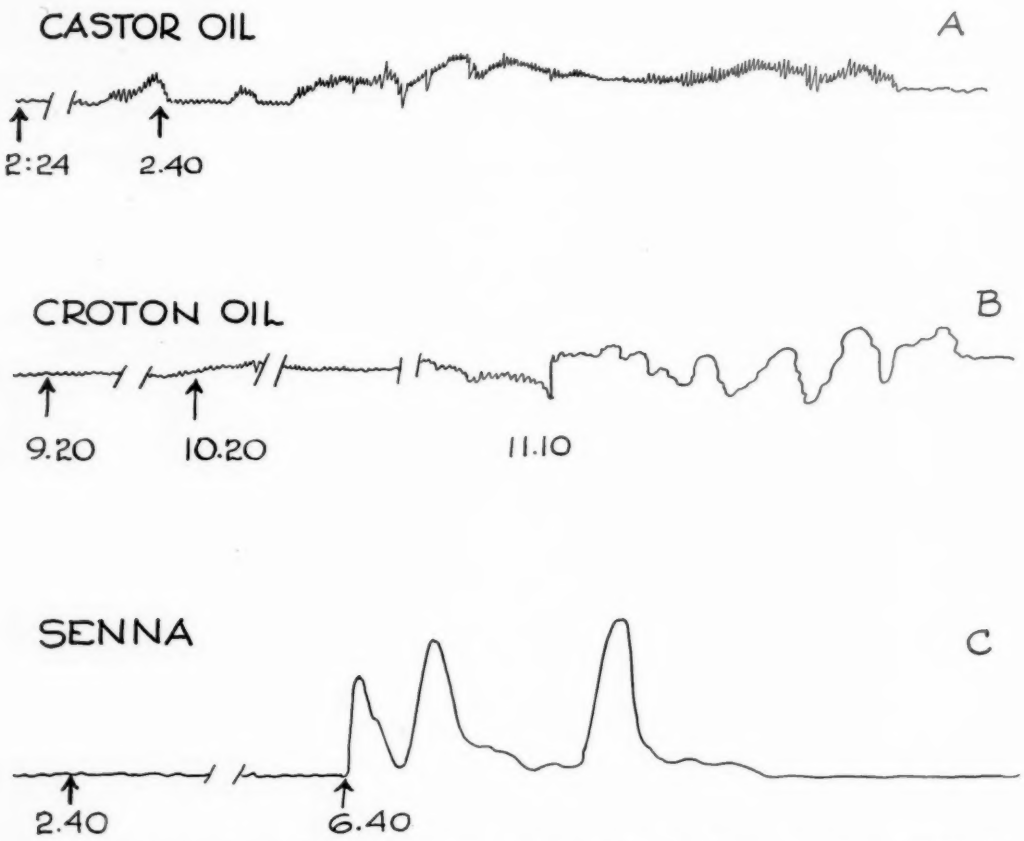

Fig. 3.—Drawing of kymograph tracings showing intracecal pressure changes following use of cathartics. The first arrow marked the time of administration of the cathartic. *A*, Castor oil: marked hypermotility with small pressure changes. Pressure range 9 to 26 cm. H_2O. *B*, Croton oil: Hypermotility and greater pressure elevation. Pressure range 6 to 33 cm. H_2O. *C*, Senna: pressure elevations without hypermotility. Pressure range 4 to 36 cm. H_2O.

D. *Tensile Strength of the Healing Appendiceal Stump.*—Bursting pressure of the normal dog cecum in 10 specimens ranged from 413 to 583 mm. Hg, with a mean of 486. Rupture usually occurred along the antimesenteric border of the cecum.

Bursting pressures of the postoperative appendiceal stump were determined in 34 animals. There was no significant difference in tensile strength between the animals with inverted and noninverted stumps.

The appendiceal stumps were found weakest on the third, fourth, and fifth postoperative days, when reductions in tensile strength of 65 to 76 per cent below the mean bursting pressure of the normal cecum occurred. On the first and second postoperative days, there was little reduction in tensile strength, emphasized by rupture of adjacent intestinal wall before rupture of the appendiceal stump in 3 of the 4 animals. Tensile strength of the stump was found increased on the sixth postoperative day, although the appendiceal site ruptured in both instances. However, on the seventh and eighth postoperative days, the surrounding intestine again ruptured first in 3 of 4 experiments.

DISCUSSION

Intracecal pressure elevations of great magnitude occur with enemas and with increased intra-abdominal tension due to straining. These pressure increases are additive when present simultaneously. Elevations of lesser magnitude may occur following the administration of cathartics, although it was not possible to show a significant elevation due to castor oil (Fig. 4).

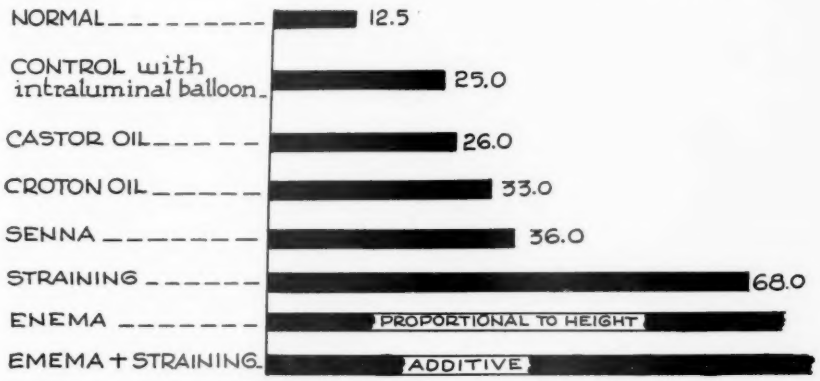

Fig. 4.—Maximal intracecal pressures (cm. H_2O) obtained after cathartics, enemas, and straining.

The danger of intracecal pressure elevation in an acutely inflamed appendix, possibly on the verge of perforation, is obvious. Boyce,[2] in a review of 8,785 cases of appendicitis, found an increasing number of complicated cases in spite of a decreasing over-all mortality, and noted that purgatives or enemas frequently had been administered to the group with complications. Foster and Edwards[5] found an extremely high incidence of cathartic administration to children with appendicitis when the diagnosis was still in doubt, and felt that this contributed to the persistent high perforation rate in their series. Catharsis incidences of 40 and 43 per cent, respectively, were found in the groups who had rupture with generalized peritonitis and rupture with abscess.

Experimental evidence, however, points to another mechanism whereby complications and mortality are increased following the use of cathartics. Dennis, Buirge, and Wangensteen[4] found that perforation in rabbit appendicitis is not hurried by purgation. Tanturi and Anderson[11] noted a high mortality following castor oil administration to dogs with experimental appendicitis, but observed that the animals died not of appendiceal perforation,

but of inability to wall off spreading peritonitis from the unperforated but gangrenous appendix. The present study has shown that marked cecal hypermotility with variable intraluminal pressure elevation may follow administration of irritant cathartics, such as castor oil or croton oil. This hypermotility of cecum and adjacent intestinal loops is probably a factor preventing localization of the inflammatory process, as previously mentioned by others.[4]

The healing of the appendectomy site in this study followed the expected pattern.[7] A lag phase of 6 days occurred, with subsequent rapidly increasing tensile strength. On the first and second postoperative days, the tensile strength was nearly normal, an effect ascribable to the unremoved sutures. On the third, fourth, and fifth postoperative days, the sutures were incapable of sealing the edematous and necrotic stump, and maximal decrease in tensile strength occurred (Fig. 5).

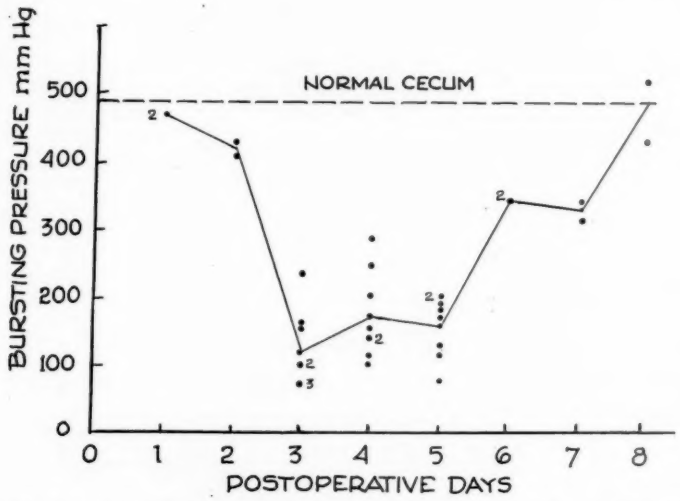

Fig. 5.—Bursting pressures of appendiceal stumps on various postoperative days. Maximal reduction in tensile strength occurred on postoperative days 3, 4, and 5.

During the period of maximum tensile strength reduction, moreover, the bursting pressures of the stump were still generally far above previously observed intracecal pressure elevations due to enemas, cathartics, and increased intra-abdominal tension. The bursting pressure of the human cecum, however, is 80 mm. Hg,[12] as contrasted to 486 mm. Hg for the dog cecum. The reduced tensile strength of the human appendectomy site could therefore easily lie within the danger zone. Enemas, cathartics, and increased intra-abdominal tension are consequently best avoided during the immediate period following appendectomy.

SUMMARY

1. Intracecal pressure elevations with enemas were directly proportional to the height of the fluid level in the enema container.

2. Intra-abdominal pressure elevations due to straining may cause marked elevation of intracecal pressure. Simultaneous straining and enemas resulted in an additive intracecal pressure effect.

3. Cathartics may produce intracecal pressure elevation, although, in this experiment, the elevation due to castor oil was small and not statistically significant.

4. Marked hypermotility of the cecum following castor oil administration was observed in 90 per cent of the animals, and is probably a factor in the increased mortality and complication rates resulting from the use of this cathartic.

5. The appendectomy site was found to be weakest on the third, fourth, and fifth postoperative days.

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THE SECRETORY ACTIVITY OF AN ISOLATED, VAGALLY INNERVATED, TOTAL GASTRIC POUCH IN MAN

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SINCE Anson and Mirsky's[2] hemoglobin method for the assay of pepsin in gastric juice was adapted to urine and blood,[21, 23] the place of these determinations in the diagnosis of gastroduodenal disease has been investigated extensively. A general relationship between the level of peptic activity in blood and urine and the presence of certain pathologic states, especially duodenal ulcer and pernicious anemia, has been established. This has created the impression that gastric secretory activity can be assessed indirectly by these measures. However, the values observed even in these conditions are characterized by wide and overlapping ranges, and frequent instances in which there are discrepancies between the results of assays of peptic activity in the three body fluids and between any of these and gastric acidity.[8, 14, 25]

The creation of an isolated, vagally innervated, total gastric pouch in a man during the course of treatment for a benign esophageal stricture provided the opportunity to study gastric secretion under conditions nearly ideal for the quantitative collection of uncontaminated gastric juice. The data were analyzed to demonstrate the diurnal variation in gastric acid and pepsin secretion, their interrelation, and their relationship to the peptic activity in plasma and urine.

CASE REPORT

The patient, C. A., a 31-year-old white man, developed an extensive stricture of the esophagus following the ingestion of a caustic solution of "carbon monoxide indicator fluid" in October, 1954. He had had no previous symptoms of gastroduodenal disease. Six weeks later a perforated anterior antral ulcer was closed by simple suture. Retrograde esophageal dilatation, initiated soon after the injury, was not successful in maintaining the caliber of the lumen above No. 28 F. Therefore, the stenosed area was bypassed with an ileocolic loop interpolated between the esophagus and the gastric antrum in September, 1955. The patient did well until Feb. 3, 1956, when a marginal ulcer of the cologastric stoma perforated. This perforation was exteriorized and on March 6 an end-to-end coloduodenostomy was performed. Difficulty of dissection and poor condition of the patient prompted the termination of the procedure by closing the pyloric canal and converting the gastric opening to a gastrostomy. The resulting anatomic arrangement, as visualized by barium contrast roentgenography, is depicted in Fig. 1.

Approximately one month after this operation, collection of the data presented here was started. During this time, and during the course of the study, the patient ate well and increased in weight from 100 to 124 pounds. He spontaneously increased his salt intake so that in spite of losing all the gastric secretion no hypochloremia or alkalosis developed. Renal function as determined by urinalyses and serum blood urea nitrogen determinations was normal. X-ray examination revealed the esophageal obstruction to be complete

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(Fig. 2). The results of stimulation of gastric secretion by insulin-induced hypoglycemia were consistent with intact vagal innervation. Therefore, except for the ileocolic "esophagus," this patient reproduced the Dragstedt pouch preparation in dogs with an isolated, vagally innervated, total gastric pouch.

The study was discontinued after one month for economic reasons. At a later date subtotal gastrectomy was performed to remove the gastric fistula. The excised portion of the stomach weighed 131 grams and represented an estimated 60 per cent of the whole. It exhibited some areas of cicatrization and infiltration by leukocytes, predominantly lymphocytes, but with many eosinophils. Otherwise it was not remarkable. Since this procedure the patient has been well. His weight has stabilized at 132 pounds and he has no nutritional problems.

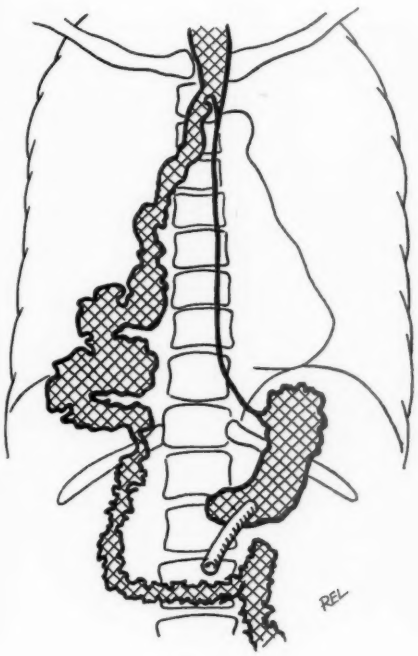

Fig. 1.

Fig. 2.

Fig. 1.—Diagram of the anatomic relationships at the time of this study as visualized by barium-contrast roentgenography. Alimentation was accomplished by way of the ileocolic segment interpolated between the proximal esophagus and the duodenum. The stomach was isolated by the acquired esophageal atresia and surgical closure of the pylorus.

Fig. 2.—Roentgenogram showing the end-to-side esophagoileal anastomosis and complete esophageal stenosis immediately below it.

METHODS

Gastric secretion was collected without suction in a disposable plastic enterostomy bag applied around the gastrostomy tube. After the evening meal the patient was fasted until the study was completed the next day, usually at noon. Twelve-hour nocturnal specimens were collected from 7 P.M. to 7 A.M., 5 days a week, followed by hourly collections throughout the morning. The "basal" secretory activity was measured from 7 A.M. to 8 A.M., when various states of stimulated or inhibited secretion were initiated. One day each week the spontaneous hourly variation during the usual test period was determined.

Simultaneously excreted 12-hour nocturnal urine specimens were obtained without catheterization. The patient was cooperative and able to void at the beginning and end of the collection period without difficulty.

An oxalated venous blood sample was drawn at 8 A.M. after each overnight study.

The peptic activity of the three body fluids was assayed immediately by modifications of the methods of Bucher[6] and Mirsky.[21, 23] The principal change in technique was the dilution of gastric juice and urine so that the level of activity was of the same order as that in plasma and could be estimated under the same conditions of incubation. This method has an experimental error of less than 5 per cent. The results are expressed in terms of tyrosine-equivalent substances liberated during 24 hours of incubation by the original undiluted specimen. The unit for gastric pepsin is a gram, for uropepsin a milligram, and for plasma pepsinogen a microgram of "tyrosine."

Gastric juice pH was measured with the Beckman pH meter and free HCl and total acid concentration determined by titration with 0.1 N NaOH, using Topfer's reagent and phenolphthalein as indicators.

RESULTS

The indicated analyses were completed satisfactorily on 24 and 23 collections of 12-hour nocturnal gastric secretion and urine, respectively, 18 specimens of 1-hour basal gastric secretion, and 22 plasma samples. The means, standard deviations of the mean, ranges, and coefficients of variation of these data are presented in Table I.

TABLE I. RESULTS OF ANALYSES OF GASTRIC JUICE, URINE, AND PLASMA

	GASTRIC JUICE		URINE	
	12-HOUR NOCTURNAL	1-HOUR BASAL	12-HOUR NOCTURNAL	PLASMA
Number of Specimens	24	18	23	22
Pepsin output (units)				
Mean ± S.D.	931 ± 310.8	132 ± 53.2	1107 ± 563.3	
Range	416 – 1464	48 – 236	264 – 2560	
C(%)*	33.4	40.3	50.9	
Pepsin (–ogen) concentration (units/ml.)				
Mean ± S.D.	2.82 ± 0.72	3.89 ± 1.00	2.58 ± 1.28	204 ± 36.4
Range	1.49 – 4.01	1.80 – 5.58	0.86 – 4.81	136 – 282
C(%)	25.5	25.7	49.6	17.8
HCl output (mEq.)				
Mean ± S.D.	42 ± 8.8	4.4 ± 1.8		
Range	19 – 63	1.5 – 8.6		
C(%)	21.0	41.1		
HCl concentration				
Clinical units				
Mean ± S.D.	128 ± 3.6	124 ± 11.4		
Range	120 – 134	90 – 135		
C(%)	2.8	9.2		
pH				
Mean ± S.D.	1.012 ± 0.045	1.014 ± 0.048		
Range	0.91 – 1.12	0.95 – 1.17		
C(%)	4.4	4.7		
Volume (ml.)				
Mean ± S.D.	329 ± 63.6	35 ± 13.2	442 ± 128.3	
Range	150 – 470	12 – 65	225 – 670	
C(%)	19.3	37.7	29.0	

*C = coefficient of variation.

The HCl concentration and pH of the gastric juice showed the least variation. The greater day-to-day variation in gastric pepsin concentration may be due either to greater error in the method of measurement (approximately 4

per cent for gastric pepsin) or less uniformity of concentration as secreted. The constancy of the results, however, compares favorably with the variation of 50 per cent reported by Osterberg and associates[24] with specimens obtained by gastric tube. The output of both acid and pepsin is more variable. The coefficient of variation for plasma pepsinogen concentration is within the range of 12 to 18 per cent reported by Mirsky.[22] The greatest variation in concentration and output is found in the uropepsin data. Although coefficients of day-to-day variation as low as 10 per cent have been reported,[14] others have found the variation to be over 100 per cent.[26] These latter results have been criticized as perhaps being due to incomplete urine collection, or deficiencies in the method of assay.[12] While the completeness of collection was not checked by creatinine determinations or catheterization, it is believed to contribute little error to these results. The pepsin assays also avoided the depreciating factors of small volume, brief incubation, and high blank values. Compared to the variation of 16 to 73 per cent (average 44 per cent) reported by Mirsky[5] for the 8-hour nocturnal uropepsin output of 5 men, the results in this patient appear acceptable.

The hourly collections of gastric secretion under varying conditions of stimulation and inhibition, in general, followed the patterns reported by others. For this reason, as well as the fact that the number of observations is too small to be significant, these results are presented only in a general manner as they illustrate certain characteristics of HCl and pepsin secretion and the relation between the two.

DISCUSSION

Mirsky and his co-workers[5] have presented evidence indicating that data for the rate of uropepsin excretion within and among healthy men are normally distributed if expressed in terms of the Briggsian logarithms of the pepsin units, but not so distributed if the arithmetic values are considered. Since conventional statistical methods are more efficient when applied to data that can be arranged in the form of a normal frequency curve, these authors advocated the use of logarithmic units. The results obtained from this patient were subjected to the same analysis with the method of Bliss[3] used for computation of the time-mortality curve. Essentially, this involves plotting individual values of pepsin output against the cumulative percentage of determinations with that or lower values, this percentage being transformed to probits. If the data are normally distributed, a straight line results. Instances in which the distribution of the arithmetic and logarithmic (or other) units differ greatly may be evaluated by inspection of the graph. The unit that produces a plot with the minimum systematic deviation from a straight line is more nearly normal in distribution and is selected for use. When the difference is not obvious, as in the present case, the rather laborious calculation of g_1 and g_2, statistics measuring asymmetry and kurtosis, respectively, and their variances may be performed to determine which distribution is closer to normal. Although usually not necessary, these calculations were made to verify the apparent discrepancy between the results depicted in Fig. 3 and those reported by Mirsky. The statistics involved in the comparison of the two units of measure, not only for uropepsin excretion but

also for gastric pepsin secretion and plasma pepsinogen concentration, are listed in Table II. In every instance the probability of a statistically significant deviation from a normal distribution was less with the arithmetic than with the logarithmic units.

TABLE II. ANALYSIS OF THE DISTRIBUTION OF PEPSIN VALUES EXPRESSED IN ARITHMETIC AND LOGARITHMIC UNITS

	ARITHMETIC		LOGARITHMIC	
SPECIMEN	ASYMMETRY g_1/S.E. g_1	KURTOSIS g_2/S.E. g_2	ASYMMETRY g_1/S.E. g_1	KURTOSIS g_2/S.E. g_2
Gastric Juice				
12-hour	+0.180	−1.270	−0.623	+52.766
1-hour	+0.842	−0.686	−4.981	+14.520
Urine	+1.321	+0.664	−1.640	+ 2.190
Plasma	−0.725	+7.984	−1.459	+13.222

When the ratio of g_1 or g_2 to its standard error (S.E.) exceeds 1.960, there is less than 1 chance in 20 that the unit of measurement that has been used in the computation is distributed normally insofar as can be judged from the experiment in question.

A negative value of g_1 indicates an excess of values smaller than the mean and a positive value an excess of values larger than the mean.

A positive value of g_2 indicates an excess of values near the mean and far from it with a deficiency of moderate deviations as compared to the normal distribution. Conversely, a negative value describes a flat-topped curve with an excess number of moderate deviations.

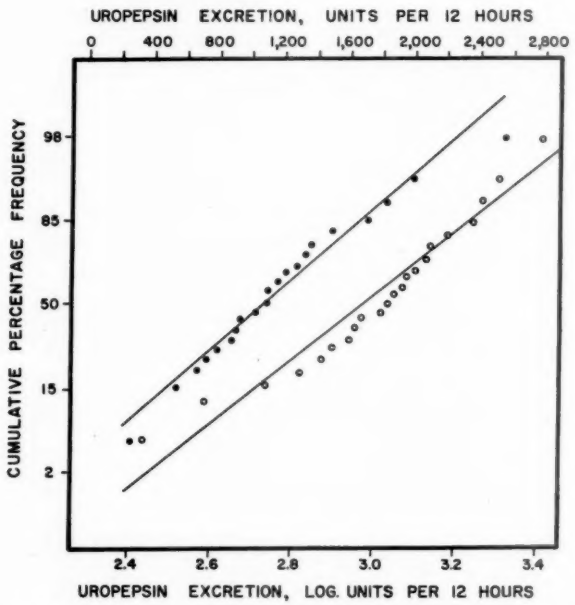

Fig. 3.—Probit plots of 12-hour uropepsin excretion in terms of units (solid circles) and logarithms of units (open circles). The straight lines have been fitted mathematically by the method of Bliss. The slight systematic deviation of the arithmetic units from the straight line has been overcorrected by the logarithmic transformation.

An explanation for this difference in results is not available. The number of observations, although small, and their range are comparable in both studies. Differences in the sensitivity and range of the assay methods employed may be responsible. In any event, this statistical analysis offers no justification for the logarithmic transformation and accordingly the arithmetic unit is used.

Comparisons between the gastric secretion, plasma pepsinogen concentration, and uropepsin excretion in this patient and in 24 duodenal ulcer and 11

nonulcer patients, studied during the same period, were made (Table III). The latter were studied in the same way as the experimental subject except that gastric juice was collected by continuous nasogastric tube aspiration. The wide variation in results apparent among the control and ulcer subjects is due partly to the small numbers involved and partly to 2 or 3 patients in each group who had levels of secretion markedly divergent from the median.

TABLE III. COMPARISON OF THE GASTRIC SECRETORY ACTIVITY OF PATIENT C. A. AND PATIENTS WITH AND WITHOUT DUODENAL ULCER

	PATIENT C. A. MEAN ± S.D.	CONTROL MEAN ± S.D.	DUODENAL ULCER MEAN ± S.D.
Gastric juice, 12-hour			
Volume (ml.)	329 ± 63.6	510 ± 532.3	702 ± 390.3[c]
pH	1.01 ± 0.04	3.24 ± 1.84[c]	2.14 ± 1.44[c]
Free HCl concentration (clinical units)	128 ± 3.6	21 ± 19.4[c]	46 ± 27.3[c]
Free HCl output (mEq.)	42 ± 8.8	13 ± 16.8[c]	40 ± 36.0
Pepsin output (units)	931 ± 310.8	702 ± 1,114.5	1,394 ± 912.5[a]
Urine, 12-hour			
Pepsinogen output (units)	1,107 ± 563.3	2,827 ± 2,470.1[b]	5,823 ± 4,041.7[c]
Plasma			
Pepsinogen concentration (units/ml.)	204 ± 36.4	396 ± 151.5[c]	557 ± 162.8[c]

Difference of the mean from that of Patient C. A. significant at the level of probability of: a, <0.05; b, <0.01; c, <0.001.

The secretory activity of the gastric pouch was within the range of control subjects. This is consistent with the absence of any ulcer history before the incident leading to this patient's hospitalization. The gastric ulcer that perforated early in the course of his illness very likely was due to a combination of factors among which may be numbered direct injury by the caustic solution and increased adrenocortical activity. Apparent elevation of hydrochloric acid concentration and output to or above the levels seen in duodenal ulcer patients resulted from the lack of dilution and neutralization by swallowed saliva and regurgitated duodenal content. The lower values for uropepsin excretion and plasma pepsinogen concentration in patient C. A. as compared to control subjects may indicate a reduction in gastric mucosal mass secondary to the injury, but could represent merely extremes of the range found among normal subjects.

HCl Secretion.—It is generally agreed that the parietal cell secretion has a constant acidity. Hollander and Cowgill[15] demonstrated by a discontinuous method of gastric juice collection from isolated canine pouches that avoided irritation by an indwelling tube or cannula, the maximum obtainable acidity and hence a close approximation of the true acidity to be pH 0.91 ± 0.02 (equivalent to 0.15 N HCl). They found this upper limit of acidity to be independent of the secretory rate and concluded that variations from this value, seen even in secretion from isolated pouches, was due to (1) dilution of acid by mucus and peptic secretion and (2) neutralization by bicarbonate entering the gastric lumen

in lymph. The values for the highest acidity among all the 1-hour fractional collections from this patient were pH 0.90, free acid 0.146 N and total acid 0.152 N. This is somewhat lower than the maximum reported by these authors because of the presence in the stomach of an indwelling catheter and the fact that no deliberate attempt was made to stimulate secretion to its limit. The results, however, coincide with those reported by other workers in studies of patients with gastric fistulas.[15] The data, as exemplified by that for free acid in Fig. 4, also demonstrate the independence of acidity and rate of secretion.

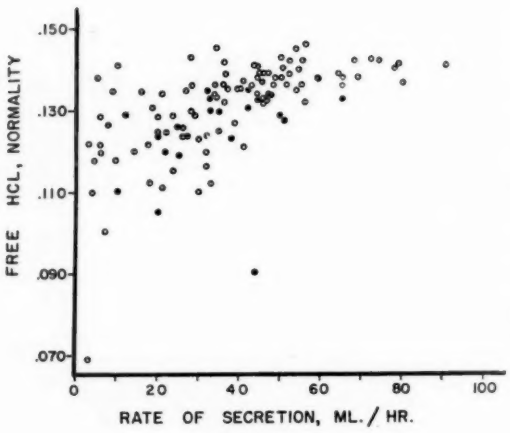

Fig. 4.

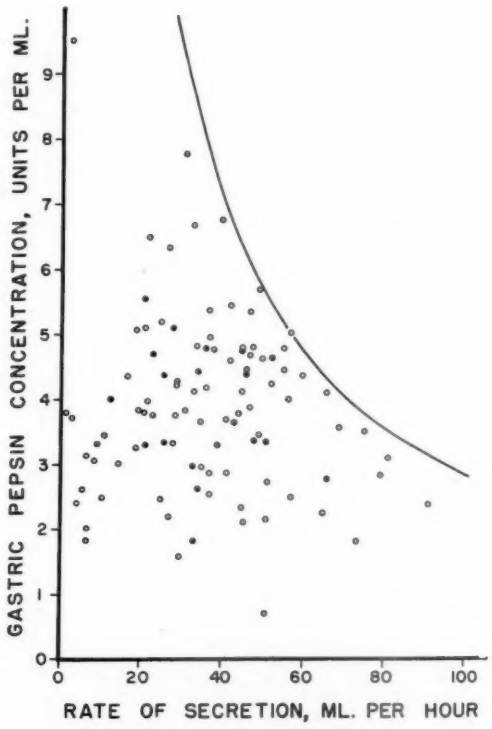

Fig. 5.

Fig. 4.—Plot of the hourly volume of gastric secretion against its titratable hydrochloric acid concentration. Specimens represented by solid circles were obtained in the basal state, those by open circles under various conditions of depressed and stimulated secretion. A plot of total acid concentration and secretory rate has an almost identical distribution but approximately 0.01 N greater concentration of acid throughout.

Fig. 5.—Plot of the hourly volume of gastric secretion against its pepsin concentration. Specimens represented by solid circles were collected in the basal state, those by open circles under various conditions of depressed and stimulated secretion. The line represents the isopleth of the maximum observed hourly pepsin output of 280 units.

Pepsin Secretion.—Osterberg and associates[24] reported that a "considerable positive (but not linear) correlation between the concentration of pepsin and volume" of secretion was present among individuals during fasting as well as after a test meal or histamine stimulation. In the present study there is no significant correlation between these variables either in the 12-hour nocturnal ($r = +0.053$, $P > 0.8$) or the 1-hour basal ($r = -0.248$, $P > 0.2$) specimens. A plot of the hourly volume of secretion against pepsin concentration in the same fractional specimens mentioned above reveals a distribution greatly different from that seen with HCl concentration (Fig. 5). It is apparent that the

concentration of pepsin is not independent of the secretory rate. Instead, it is the maximum hourly output (280 units in this case) as represented by the line, that appears to have a definite limit unrelated to the volume of secretion. Coordinates on and close to this line were measured under conditions in which pepsin secretion is known to be stimulated, namely, during insulin hypoglycemia and following the injection of histamine and caffeine. Plotting the "nonparietal" secretory rate and pepsin concentration, calculated on the basis of the measured output and constant normality of acid, does not alter the distribution of these points. This supports the view that at least most of the water as well as the enzyme is added to the gastric juice by the chief cell.[12, 19] The concentration of pepsin depends upon the relative proportions of these components, which to a considerable extent can be dissociated.[12, 13]

Correlation of Gastric Pepsin and HCl.—Good positive correlation between gastric pepsin and HCl among individuals has been demonstrated repeatedly.[1, 8, 18, 26] Book and his co-workers,[4] however, did not confirm this, and Poliner and Spiro[25] have emphasized the independence of secretion of these gastric juice components. Examination of the data involved in two of the studies that show a significant correlation reveals it to be heavily weighted by a few subjects with hypersecretion and many with achlorhydria or achylia.[1, 18] When these values are eliminated, little or no correlation remains. This is consistent with the conclusion that pepsin and HCl are secreted independently, albeit in response to the same stimuli acting through different mechanisms.[13, 16, 18, 29] The proportion of each, then, could be expected to vary depending upon the functioning mass of chief and parietal cells which is subject to normal and pathologic variation.

Hirschowitz[13] has shown further that the pepsin/hydrogen ion correlation is constant in the individual under all conditions of basal, depressed, and stimulated secretion except those of hyperventilation and Diamox (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) administration. In the latter circumstances, hydrogen ion output is depressed while pepsin secretion is increased. This constancy is demonstrable in the basal and variously stimulated secretion of this patient collected in hourly fractions. In the upper portion of Table IV are grouped the conditions under which the pepsin/HCl output correlation is statistically significant at the 1 per cent or better level of probability. Analysis, after transforming r to z and weighting for unequal numbers, shows that these coefficients could all come from the same population, ρ, which is estimated as +0.802. The individual coefficients in the lower part of the table are not statistically significant as might be expected from the small number of observations involved. However, they also could be drawn from a common correlation population with $\rho = +0.730$, which is not significantly different from that of the first group ($P > 0.4$). Combining all the coefficients yields an estimate of $\rho = +0.794$ with 0.95 confidence limits of +0.710 to +0.856. Analysis of the 103 individual coordinates, irrespective of the conditions under which they were observed (Fig. 6), gives a correlation coefficient of +0.738.

TABLE IV. CORRELATION OF GASTRIC PEPSIN AND HYDROCHLORIC ACID OUTPUT IN BASAL AND VARIOUSLY STIMULATED SECRETION

CONDITIONS OF SECRETION	NUMBER OF SPECIMENS n	COEFFICIENT OF CORRELATION r	PROBABILITY* P
Basal	20	+0.762	<0.001
Fasting	18	+0.750	<0.001
Histamine	9	+0.854	<0.01
Insulin	9	+0.894	<0.01
Histamine and insulin	10	+0.796	<0.01
ACTH	8	+0.854	<0.01
Average	+0.802	$\chi^2 = 1.403$	$P = 0.92$
Food (mixed)	4	+0.832	>0.1
Fat	4	+0.714	>0.2
Glucose	4	+0.660	>0.3
Water	5	+0.360	>0.5
Alcohol	4	+0.923	>0.05
Caffeine	4	+0.872	>0.1
Glucagon	4	+0.682	>0.3
Average	+0.730	$\chi^2 = 1.339$	$P = 0.959$
Grand average	+0.794	$\chi^2 = 2.958$	$P > 0.995$
Confidence limits (0.95)		$+0.710 \leq \rho \leq +0.856$	

*Probability of a larger r in sampling from a bivariate normal population with a correlation coefficient, $\rho = 0$.

Inhibition of secretion by the anticholinergic drug Pro-Banthine (propantheline bromide) was studied in one experiment only. Since there was no gastric output during the second and third hours after injection, the number of determinations is inadequate for analysis. Inhibition occurred in other tests, however, principally in the first hour after injection of ACTH or caffeine or the ingestion of fat, during the third hour of continued fasting (10 to 11 A.M.) and after glucagon* injection, and during the fourth and fifth hours after a single injection of insulin. In each instance there was reduction of secretion to 10 ml. or less per hour, increase in viscosity of the gastric juice, and cessation of hunger although the patient continued to fast. The mechanism by which secretion was depressed probably varied to include reflex inhibition due to pain, vasoconstriction, endogenous enterogastrone,[10] and hyperglycemia.[20] Nevertheless, the pepsin/HCl correlation of +0.676 is significant ($P < 0.05$) and does not differ significantly from that of the stimulated secretion ($P > 0.4$).

No significant correlation between HCl output and either the plasma concentration or the urinary excretion of pepsinogen is demonstrable.

CORRELATION OF GASTRIC PEPSIN AND PLASMA PEPSINOGEN AND UROPEPSIN

It has been established, by indirect evidence at least, that a fraction of the pepsinogen output of the chief cell enters the blood and is excreted as urinary pepsinogen, more commonly designated uropepsin. The possibility of estimating gastric secretory activity indirectly by measuring plasma pepsinogen concentration or uropepsin excretion is attractive. Such a procedure would obviate the need of gastric intubation with its accompanying discomfort to

*Supplied by Dr. W. R. Kirtley, Eli Lilly & Company, Indianapolis, Ind.

the patient and avoid errors due to the variable effect on secretion of the tube itself, incomplete collection of gastric juice, and contamination with regurgitated duodenal contents, especially following surgical procedures on the stomach.

Statistically significant positive correlation between mean gastric pepsin output and plasma pepsinogen concentration among individuals has been reported.[8, 11] This also is observed between the single observations in the duodenal ulcer and control patients examined concurrently with the subject of this study ($r = +0.538$, $P < 0.01$). However, this statistic is heavily weighted by five low coordinates. If these are eliminated, the remaining show little correlation. The same criticism applies to the correlation of +0.603 ($P < 0.001$) between mean values reported by Hirschowitz.[11] Although there

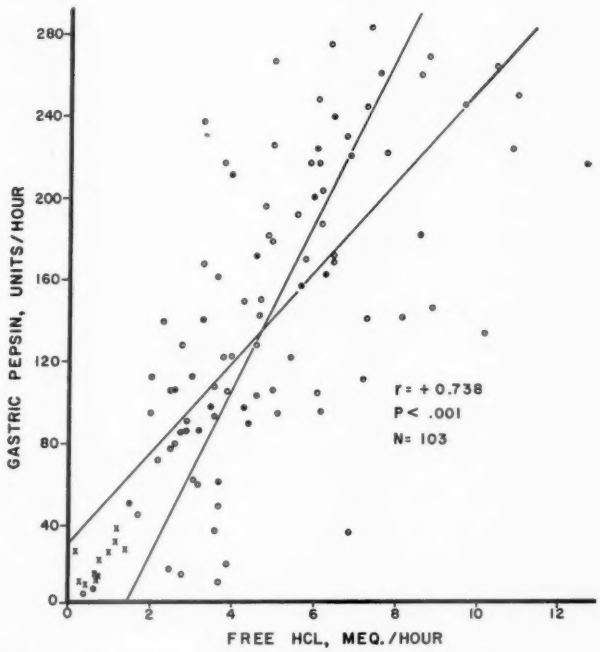

Fig. 6.—Plot showing the correlation between the outputs of pepsin and titratable hydrochloric acid in 1-hour specimens of gastric juice. Specimens represented by solid circles were collected in the basal state, those by open circles under various conditions of depressed and stimulated secretion. The coordinates shown as crosses are those specimens with a volume of 10 ml. or less (see text).

is an obvious good correlation among five "high secretors," there is little or no correlation among the 13 "low secretors." When 64 coordinates from the 18 subjects are considered together, removal of 4 representing highest gastric secretion renders the correlation insignificant. The other report does not contain sufficient data to evaluate the validity of the coefficient ($r = +0.508$, $P = 0.01$). Within the single subject of this study there is no correlation between plasma concentration and 12-hour ($r = -0.302$, $P > 0.1$) or 1-hour ($r = -0.036$, $P > 0.8$) gastric output of pepsin. The negative coefficient of the 12-hour specimens that approaches significance is of interest. Although it may be due entirely to chance, this relationship could result from superficial gastritis in

which the ostia of the tubules are obstructed by the inflammation, thus impeding the external secretion of pepsin while increasing the passage of the proenzyme into the blood through defects in the tubular wall.[25]

Similarly, positive correlation has been reported between gastric pepsin and uropepsin.[1, 8, 19] Among the control and ulcer patients this is +0.655, $P < 0.001$. Again, however, this statistic, as well as those reported by some others,[1, 17] is dependent upon a relatively small number of coordinates at the extremes of the distribution without which they are not significant. Other authors[14, 26, 29] have found no good correlation among individuals. In the present study of a single subject 12-hour uropepsin excretion is not related significantly to gastric pepsin secretion in 12-hour ($r=-0.139$, $P > 0.5$) or 1-hour ($r=-0.201$, $P > 0.4$) collection periods.

This inconsistency or relatively poor degree of correlation between gastric pepsin output and plasma concentration or urinary excretion is understandable on the basis of what little is known about the origin and elimination of the plasma proenzyme. Its concentration obviously depends upon the rate of gastric endocrine secretion, its distribution in body fluid compartments, and the rate of renal excretion. The available data on the relationship of the internal to external secretion of pepsin have been interpreted in two ways.[8, 12] First, it has been postulated that the normal turnover of mucosal cells results in disintegration of chief cells with liberation of proenzyme which is absorbed from the interstitial fluid. Thus, in the case of a normal stomach, the "endocrine" secretion varies with the mass of chief cells. The exocrine secretion, on the other hand, fluctuates widely with the functional state of the cells and is unrelated to plasma pepsinogen except under conditions of maximal output which is also dependent upon cell mass. Alternatively, it has been considered that a small proportion, about 1 per cent,[17] of the pepsinogen produced is secreted directly into the blood across the cell-capillary membrane. In this way the endocrine secretion could reflect the peptic activity of the stomach. The failure of isolated determinations of plasma pepsinogen to follow the external output can be explained by the diffusion of this small amount of proenzyme into the entire extracellular and at least part of the intracellular fluid space. Hence, the means of serial assays of the gastric and plasma enzyme correlate better than single determinations[11] and the results following prolonged or repeated gastric stimulation better than after brief stimulation.[8, 27, 28]

The renal excretion of pepsinogen affects the plasma level and in turn is influenced by it, as well as by other variables. The pepsinogen clearance parallels, but is lower than, that of creatinine.[14] It has not been established that this difference is caused by a lower glomerular filtration of the proenzyme, due to its molecular configuration or to tubular reabsorption. In cases of renal insufficiency the plasma concentration may be elevated and the clearance decreased.[28] The high plasma pepsinogen levels of duodenal ulcer patients, when considered as a group, are associated with correspondingly increased uropepsin excretion but a normal clearance rate.[14] The administration of

ACTH and most adrenocortical hormones, however, increases the renal clearance. The relationship of uropepsin to gastric pepsin is further complicated by the observation of Hirschowitz and Streeten[14] that the increased clearance induced by steroids is not accompanied by increased gastric pepsin output or significant change in plasma concentration. This suggests that these hormones also alter the ratio of endocrine to exocrine secretion. However, the role of adrenocortical hormones in gastric secretion in man still is unresolved. Gray and his associates[9] have reported a direct stimulant action while Hirschowitz[12] favors a trophic or permissive role.

The results of this study serve to emphasize the point made by other investigators[8, 25, 29] that gastric secretion of acid or pepsin cannot be measured indirectly by determination of the plasma concentration or urinary excretion of pepsinogen. These variables frequently are found to be related in a general way,[1, 7, 8, 11, 17] probably because of their ultimate dependence upon the gastric mucosal cell mass[12, 29] and its general response to a given stimulus[13, 18, 27, 29] or change in a common factor such as vascularity.[16] Hence, the determinations are of value in some clinical situations including the evaluation of patients from whom it is not possible to obtain gastric juice or in whom the secretion is contaminated by blood or small intestinal content, and as a preliminary test in screening patients for achylia. However, because of the individual and diurnal variation caused by the largely uncontrollable and incompletely understood factors mentioned above, the results of such analyses must be interpreted with caution and cognizance of their uncertain relationship to gastric secretion.

SUMMARY

The production of an isolated, vagally innervated, total gastric pouch in man incidental to the treatment of a benign esophageal stricture has afforded an opportunity to study gastric secretory activity with nearly ideal conditions of gastric juice collection. Comparison of this subject to duodenal ulcer and nonulcer patients studied concurrently indicates that the secretory activity of the pouch was in the low normal range.

Statistical analysis of data from assays of peptic activity in gastric juice, plasma, and urine does not justify transformation from arithmetic to logarithmic units as suggested for uropepsin by others.

The independence of hydrochloric acid concentration from secretory rate is confirmed. The secretion of pepsin differs from that of acid in that the rate appears to have a finite limit independent of the volume, while the concentration varies with the level of water secretion which may be dissociated from that of the enzyme.

Under all conditions of secretion studied, that is, basal, stimulated, and depressed, the pepsin/HCl correlation in this individual did not vary significantly. Differences in this measure between individuals have been reported and explained on the basis of variations in gastric mucosal cell population.

Statistically significant positive correlations between the plasma concentration and urinary excretion of pepsinogen and the gastric pepsin and acid

secretion are demonstrable within groups of individuals, especially if low and high secretors are included, and the means of serial observations are analyzed. This relationship does not persist when the diurnal variations of a single subject are considered.

The status of gastric secretory activity cannot be measured indirectly by determination of plasma concentration or urinary excretion of pepsinogen alone. These assays, however, frequently are valuable in assessing gastric secretion in its entirety and are of assistance in the diagnosis of gastroduodenal disease if their limitations are recognized.

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USE OF TEFLON MESH IN THE REPAIR OF MUSCULOFASCIAL DEFECTS

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HERNIA is probably the most common surgical disorder found in man, accounting for 10 to 15 per cent of all surgical admissions to the hospital[2] and being the principal cause of rejection of registrants during World War II.[10] Recurrence rates following surgery are between 5 and 10 per cent for inguinal hernias and approximately 20 per cent for postoperative hernias.[1, 8, 11-19] Seventy-five per cent of these recurrences appear within the first 2 years after surgery.[5] While it is true that hernia is not often a cause of death, when total morbidity and economic loss to society is tallied, it assumes extreme importance. To confront this problem, especially in patients with poor fascial tissues or large defects, a good fascial substitute would be a great boon to the surgeon.

The ideal fascial substitute has yet to be found. Such a substance should be (1) biologically nonirritating to tissues, (2) of inorganic nature, (3) easily sterilized and not altered by sterilization, (4) chemically inert in tissue fluids, (5) pliable and nonrigid so as to adjust to tissue movement, (6) strong enough to withstand local stress and intra-abdominal pressure, (7) nonelectrolytic, (8) not subject to fragmentation or becoming "work hardened," (9) available and inexpensive, (10) nonhygroscopic, and (11) nonopaque to x-ray. To these criteria laid down by Floyd,[3] we would like to add, (12) ability to maintain itself and become incorporated by connective tissue, despite the presence of infection, as long as there is adequate drainage.

For over a year we have been working with the new plastic polytetrafluorethylene (Teflon*) as a fascial substitute, first in dogs and then in human patients. This experience has encouraged us to the point where we feel that Teflon may be the best material available for repairing large and difficult hernias with poor local tissues. It has definite advantages over tantalum and stainless steel mesh, which tend to become work hardened and fragment in from 6 to 10 months, and is superior to the other plastics tried to date. Teflon also comes very close to meeting all the requirements just outlined.

CHARACTERISTICS OF TEFLON

Teflon (polytetrafluorethylene) is one of the most inert plastics yet discovered. Its most unique characteristic is its nonwettability. It cannot be wet with water and practically nothing will adhere to it. Its tenacity is 1.6 to 2.0

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*Teflon is Du Pont's registered trade-mark for its TFE-fluorocarbon fiber.

grams per denier; elongation at break is 15 to 33 per cent; it is not affected by moisture, heat up to 400° to 500° F., or age; and it is inert to acids, alkalies, organic solvents, bacteria, and fungi.[4] It is attacked only by molten alkali metals and fluorine gas at elevated temperatures and pressures.[6]

LeVeen and Barberio[9] experimentally tested the tissue-exciting qualities of celluloid, Lucite, nylon, and Teflon by intraperitoneal instillation of the finely divided foreign materials. The surface areas of both the foreign substances and the tissues exposed are important factors in determining tissue reaction. They found that celluloid, Lucite, and nylon were all potent exciters of tissue reaction. Teflon, on the other hand, showed no evidence of gross tissue reaction. The particles of the first three plastics were all surrounded with absorbed water and protein, just as Knisely's India ink particles were coated with a protein material prior to phagocytosis. This was not true with the Teflon particles. LeVeen felt that the absorption of protein by plastics which are wettable may similarly stimulate production of giant cells and proliferative fibrosis, accounting for the difference.

Girvin, Wilhelm, and Merendino[4] demonstrated that Teflon fabric, used as arterial grafts in dogs and left in place over 300 days, did not lose strength. Harrison[6] reported actually increased strength of grafts implanted 208 days as arterial grafts and 301 days as pericardial grafts. Nylon, on the other hand, loses about 80 per cent of its strength in 6 months due to hydrolysis and chemical deterioration. The Instron apparatus was used for this testing. With this apparatus, full-scale sensitivities from 2 grams to 1,000 pounds can be measured with accuracy better than 0.5 per cent.

Harrison recently reported the use of Teflon fabric as a fascial replacement.[7] He implanted a loose weave and a close weave Teflon fabric in clean and infected defects created in 41 dogs. Tantalum wire mesh was used in each case as a control. In the clean wounds, all the grafts did well; however, the looser weave tantalum and Teflon did slightly better. In the infected wounds, there was good healing in those repaired with tantalum wire mesh and the loose weave Teflon fabric which was comparable to the tantalum in its looseness of weave. In these cases the close weave Teflon grafts all failed. They did not allow adequate drainage or rapid enough growth of fibrous tissue to isolate the individual fibers, a necessity for healing in the presence of infection. His conclusions were that an open weave Teflon, of equal porosity to tantalum mesh, is superior to tantalum mesh because of its pliability and strength over long periods.

Teflon materials are easily prepared for surgical use by washing in water and detergents to remove plasticizers, and they can be autoclaved as many times as necessary. The fabric as available is brown in color, but can be completely decolorized by boiling in concentrated nitric acid for 24 hours; however, in our experience, this offers no advantage.

OUR EXPERIENCE USING TEFLON MESH AS FASCIAL SUBSTITUTE

Our interest in the use of Teflon as a fascial substitute was first carried to the dog laboratory where we sought to confirm previous reports. We used

close, medium, and loosely woven Teflon fabrics to repair surgically created fascial defects in dogs. These experiments confirmed the highly inert nature of Teflon to animal tissues and demonstrated again the advantages of the loose weave material. They could be incorporated rapidly and completely with fibrous tissue whereas the closely woven fabrics tended to prevent this healing process.

From April 19, 1957, to Dec. 12, 1957, we used Teflon prostheses in 26 patients with difficult hernias. All of these patients were on the surgical service of the Wadsworth General Hospital at the Veterans Administration Center in Los Angeles. Of these patients, 13 had postoperative abdominal hernias, four of which had been repaired two or more times previously: Stainless steel and tantalum mesh had been used in 2 of these cases. There were 13 inguinal hernias, all of which were recurrent except in the case of one obese patient with bilateral direct and indirect hernias and chronic bronchitis. There was also one large spigelian hernia and a recurrent femoral hernia.

In these patients, we again made use of the three Teflon fabrics used previously in the animal experiments, and, in addition, two new loosely woven fabrics especially prepared for us so as to prevent fraying at the cut margins.* Fig. 1 pictures the comparative weaves of these fabrics.

These 26 patients have now been followed from 6 to 12 months without recurrence of their hernias. Tables I, II, and III summarize these cases. The average age of the patients was 60 years; the youngest was 33 years old, and the oldest 85 years. Of the 10 patients with recurrent inguinal hernias, 4 of them had chronic pulmonary conditions with cough. One had lost over 40 pounds secondary to family difficulties and worry. The patient with the recurrent femoral hernia had chronic bronchitis, emphysema, and polycythemia. Eleven of the 13 patients with postoperative abdominal hernias had histories of wound infection complicating their antecedent surgery. Four of the hernias appeared after cholecystectomies, 5 after subtotal gastrectomies, one after a vagotomy and pyloroplasty, one following appendectomy, and one following blunt external trauma to the abdomen during World War II.

METHOD OF SURGICAL REPAIR WITH TEFLON MESH

For the inguinal hernias, the Teflon grafts were used to reinforce the transversalis fascia, or replace it if deficient. In many instances, the inguinal ligament was deficient or too attenuated from previous repairs to use, so a Cooper's ligament repair was done. If the inguinal ligament was adequate and no weakness of the femoral canal was present, a Bassini or Halsted type of repair was carried out. Most of our grafts were sutured in place with either No. 35 stainless steel wire or silk sutures. In case of infection, the silk sutures can be a source of trouble.

The majority of the patients with postoperative hernias were in the older age group and many were in poor physical condition because of accompanying cardiovascular and pulmonary diseases. Some of their defects were too large to expect the fascial margins to approximate without marked preoperative weight

*John Sidebotham Co., Inc., Philadelphia, Pa.

reduction, generous relaxing incisions and a tight repair at surgery, running the risk of weakening the abdominal wall even further and having a high recurrence rate. With these factors in mind, we tried to work out a method of repair that would require a minimum of time and dissection and yet give a strong repair. This method is not original with us, but it is simple and easy to carry out. No attempt is made to dissect out the various abdominal layers.

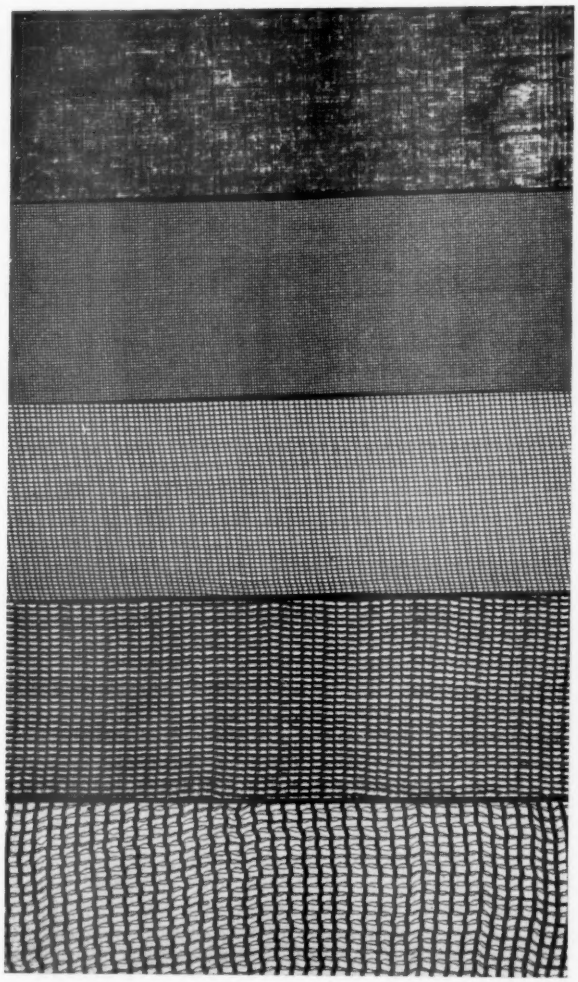

Fig. 1.—Comparison of the 5 Teflon weaves used in this study. *From top to bottom:* close weave, medium weave, loose weave, and two loose weave, nonfraying Teflon meshes.

These large hernias have only a thin layer of skin and peritoneum holding the abdominal viscera. The skin and peritoneum are opened and the fascial ring is palpated and outlined. Adhesions between abdominal viscera or omentum are carefully separated to a distance of about 2 inches beyond the fascial margins around the defect. A piece of Teflon mesh is cut to appropriate size. A small cuff is turned up along the edge of the Teflon graft and the suture is placed first through this folded margin, then through the peritoneum and fascia from within out, approximately 1 cm. back from the edge of the defect to ensure a

TABLE I. INGUINAL HERNIAS REPAIRED WITH TEFLON MESH

PATIENT	AGE	TYPE OF PRESENT HERNIA	NUMBER OF PREVIOUS REPAIRS	CONDITIONS ABETTING RECURRENCE	TYPE OF TEFLON USED	TYPE AND DATE OF REPAIR	COMPLICATIONS	FOLLOW-UP ON HERNIA TO PRESENT
O. M. G.	67	Left recur.	Left 2× Right 2×	Chronic bronchitis	Close weave	Halsted 4/16/57	None	No recurrence; asymptomatic
J. L.	67	Right recur.	Bilat. 1×	Bronchitis, obesity	Close weave	McVey 4/22/57	Wound infection; draining sinus	No recurrence; asymptomatic
W. R. H.	33	Right recur.	Right 4×	Poor tissues	Close weave	McVey 7/5/57	None	No recurrence; asymptomatic
A. S.		Left recur.	Left 1×		Medium weave	Bassini 8/8/57	None	No recurrence; asymptomatic
E. W.	73	Bilat. direct	None	Bronchitis, obesity	Medium weave	Bassini 8/9/57	None	No recurrence; asymptomatic
E. E. B.	61	Left recur.	Right 3× Left 2×	Bronchitis, obesity	Loose weave	McVey 8/27/57	None	No recurrence; asymptomatic
L. S.	68	Right recur.	Right 4× Left 1×	Poor tissues	Close weave	Bassini 8/27/57	None	No recurrence; asymptomatic
H. T.	46	Left recur.	Bilat. 2×	Bronchitis, obesity	Close weave	McVey 8/27/57	None	No recurrence; asymptomatic
F. W.	85	Right recur.	Right 1×		Close weave	Bassini 8/27/57	None	No recurrence; asymptomatic
H. W.	62	Bilat. recur.	Right 2×	Poor tissues	Loose weave	Bassini 9/16/57	Hematoma; infection	No recurrence; asymptomatic
E. W. S.	64	Right recur.	Right 1×	40 lb. wt. loss	Loose weave	Bassini 9/29/57	None	No recurrence; asymptomatic

TABLE II. MISCELLANEOUS HERNIAS REPAIRED WITH TEFLON MESH

PATIENT	AGE	TYPE OF HERNIA	NUMBER OF PREVIOUS REPAIRS	CONDITIONS ABETTING RECURRENCE	TYPE OF TEFLON USED	TYPE AND DATE OF REPAIR	COMPLICATIONS	RECURRENCES
G. W. R.	57	Right recur. femoral	3×	Bronchitis; emphysema	Medium weave	McVey 6/12/57	None	None
F. G. D.	73	Left spigelian	None		Loose	See Fig. 2	None	None

TABLE III. POSTOPERATIVE VENTRAL HERNIAS REPAIRED WITH TEFLON MESH

PATIENT	AGE	OPERATION CAUSING HERNIA	SIZE OF FASCIAL DEFECT	NUMBER OF PREVIOUS REPAIRS	CONDITIONS ABETTING P.O. HERNIA	DATE OF OPERATION AND TYPE TEFLON	COMPLICATIONS	RECURRENCE OF HERNIA REPAIRED
J. S. P.	47	Cholecystectomy, 8 yr. before	3 × 4 cm.	1	P.O. wound infection	5/22/57 Close weave	None	None
A. J. B.	39	Subtotal gastrectomy, 8 yr. before	17 × 10 cm.		P.O. wound infection	7/25/57 Close weave	None	None
O. W.	77	Cholecystectomy, 5 mo. before	17 × 10 cm.		P.O. wound infection	7/29/57 Close weave	None	None
W. J. P.	60	Cholecystectomy, 5 mo. before			P.O. wound infection	7/31/57 Medium weave	None	None
R. B. L.	63	Suprapubic prostatectomy, 2 yr. before	11 × 12.5 cm.		P.O. wound infection	8/15/57 Close weave	None	None
P. W. L.		Subtotal gastrectomy, 3 yr. before	7.5 × 11 cm.		P.O. wound infection	9/4/57 Close weave	None	None
R. J. H.	37	Appendectomy, 24 yr. before	5 × 8 cm.		P.O. wound infection	9/12/57 Close weave	P.O. draining sinus	None
H. J. P.	60	Subtotal gastrectomy, 4 mo. before	6.5 × 11 cm.		P.O. wound infection	9/18/57 Close weave	None	None
S. J.	59	Subtotal gastrectomy, 3 yr. before	7.5 × 12 cm.		P.O. wound infection	9/26/57 Close weave	None	None
J. K. B.	61	Subtotal gastrectomy, 4 yr. before	14 × 18 cm.		P.O. wound infection	9/27/57 Close weave	Cerebral vascular accident 4 days P.O.	None
B. L. S.	57	Blunt trauma to epigastrium		2	Poor tissues	9/27/57 Close weave	Second hernia in lower abdomen	None
J. H.	47	Transabdominal iliac node dissection	12 × 12 cm.		Deficient tissue	10/25/57 Loose weave	None	None
C. L. M.	62	Vagotomy and pyloroplasty, 5 mo. before	11 × 10 cm.		P.O. wound infection	12/12/57 Loose weave	None	None

strong bite. Allis clamps can be used by the assistant to grasp the fascial margin and turn it up, making exposure better for the surgeon. Having placed these peritoneal-fascial sutures about the circumference of the defect, the sutures are tied, pulling the graft snugly but not too tightly into the defect, without wrinkling. Any excess cuff of the graft is excised with scissors. This leaves a smooth surface of Teflon intraperitoneally. Some might worry about adhesions between Teflon and intra-abdominal viscera. From our experience we do not feel this will become a problem. The Teflon fabric is too smooth and inert for anything to stick to it easily. In one of our dogs which developed a large subcutaneous abscess between the skin and the graft, the peritoneal side of the Teflon graft formed only minimal loose adhesions with omentum and viscera.

After the prosthesis has been sutured in place, the fascial margins can be sutured over the prosthesis if this can be done without tension. If not, then the subcutaneous and skin layers are approximated over the Teflon after first excising any excess skin. At first, we placed a small catheter beneath the skin and connected it to low pressure suction for a few days to prevent fluid accumulation. We soon found that very little fluid was formed and that this step was not necessary. Since there is no extensive dissection, no large raw areas are left to ooze blood and serum. When the loosely woven porous mesh is used, any fluid formed can drain into the peritoneal cavity and be quickly absorbed. When the closely woven mesh is used, it will be necessary only occasionally to insert a needle and aspirate the small amount of serous fluid. The artist's drawings in Fig. 2 demonstrate the steps of the repair.

COMMENTS

This preliminary report contains too few cases with too short a period of follow-up to be of much value in drawing any conclusions. We present it only to report on the technical aspects of the use of Teflon. It is planned to follow the first group of patients for at least 24 months before making conclusions. Some observations on this limited use of Teflon mesh as a fascial substitute might be made, however.

As is true when any foreign material is to be incorporated into any body wound, careful surgical technique and asepsis must be used. Even though Teflon is unusually inert, still it will act as a foreign body if infection is present. This is especially true of the closely woven mesh. The closely woven mesh is too slowly incorporated with fibrous tissue to maintain itself in the presence of infection, so a chronic draining sinus will develop until the Teflon is removed. We have been pleased to note that in the case of the loosely woven mesh this may not be necessarily true. The point is illustrated in both dog experiments reported earlier and in one of our patients.

Study of Tables I, II, and III will indicate that 3 of the patients did develop wound infections, one secondary to a hematoma. This was regrettable for it demonstrated poor technique, but it did enable us to watch the reaction of the mesh to infection. In 2 of these patients, closely woven Teflon mesh had

been used. After surgical drainage of the subcutaneous space, application of warm compresses, and administration of specific antibiotics, the wounds healed without removal of the grafts, but later chronic draining sinuses developed. After a period of 4 months in one case and 6 months in the other, the grafts were removed. At surgery, it was observed that the Teflon fabric was quite intimately incorporated with fibrous tissue in some areas, despite the close weave. The inflammatory reaction was minimal. Beneath the prosthesis, a strong fibrous membrane had formed which was not disturbed. Both wounds healed promptly and completely when the grafts were removed. Follow-up periods of 6 and 8 months, respectively, have demonstrated no weakness in the repaired area despite the fact that the Teflon had been removed.

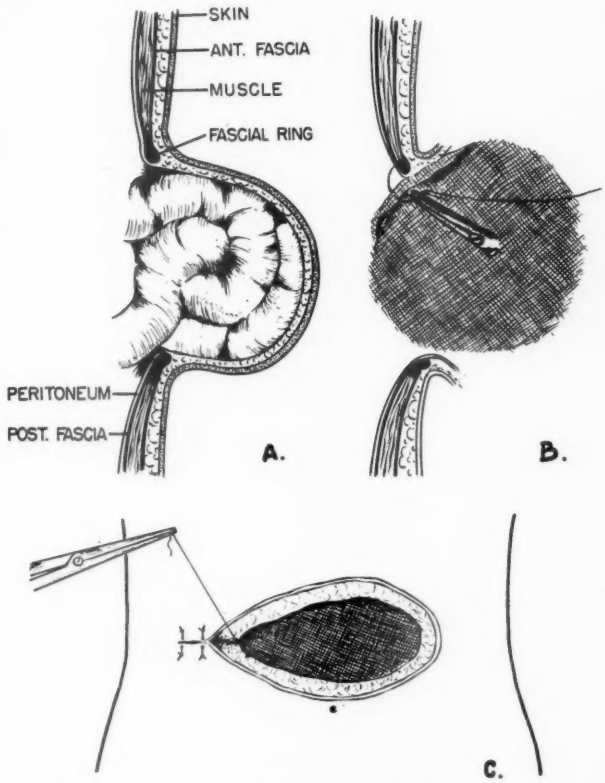

Fig. 2.—*A*, Cross section through a large ventral hernia demonstrating fascial ring and abdominal wall layers. *B*, First suture passes through folded margin of Teflon mesh and peritoneal-fascial ring in repair of defect. *C*, Subcutaneous tissue and skin layers are approximated over Teflon mesh.

In the third patient in whom infection developed, a loosely woven Teflon mesh had been used. This patient had bilateral recurrent inguinal hernias repaired. Open drainage of the subcutaneous spaces, hot compresses, and specific antibiotics were given. In this case, the wounds both healed and an 8-month postoperative check revealed the repaired areas to be strong and without evidence of infection.

In the repair of postoperative ventral hernias, the Teflon grafts should be sutured in place snugly but not too tightly. It is easy to make the repair

too tight if the patient is under spinal anesthesia or muscle relaxant drugs. A smooth postoperative course not complicated by excessive retching or coughing should be planned in advance.

SUMMARY

Teflon is the most inert of the plastic materials studied to date. It is stable against hydrolyzing and oxidizing agents and its wettability is nil, preventing its deterioration in tissue fluids. Implantation in body tissues up to one year reveals no loss of strength, while nylon loses about 80 per cent of its strength due to hydrolysis and chemical deterioration. Teflon fabrics can be easily prepared for surgical use by washing in detergents to remove plasticizers and can be autoclaved as many times as necessary.

Our animal experiments with Teflon convinced us of the superiority of the loose weave Teflon fabrics which can be quickly and completely incorporated with fibrous tissues, while the tightly woven fabrics tend to prevent this healing process. The absence of inflammatory cells is noteworthy. A new loose weave fabric, especially woven to prevent fraying, has been used. In case of infection, this loosely woven fabric with large interstices has a chance of maintaining itself without being extruded or forming a draining sinus, as long as cotton or silk sutures are not present. Rapid connective tissue growth about each Teflon thread isolates the graft from the infection, allowing the wound to heal.

Twenty-six patients with difficult hernias had them repaired with Teflon prostheses. There were 13 postoperative abdominal hernias and 13 inguinal hernias, 11 of the latter being recurrent. There was one recurrent femoral hernia and one spigelian hernia. These patients have all been followed from 6 to 12 months without recurrence of any of the hernias during this preliminary period. The methods of repair have been described, including a simple method of repairing large ventral hernias with inadequate tissues.

It is our opinion that Teflon is a promising fascial substitute, superior to other plastic materials used heretofore, and having many advantages over tantalum mesh. These advantages are its ease of handling, its availability and low cost as compared with tantalum, its proved strength in body tissues over long periods without chemical deterioration or fragmentation, and its inertness to body tissues which equals that of tantalum. In case of re-operation for other intra-abdominal conditions, Teflon need not be removed as would be the case with tantalum, and it is nonopaque to x-ray.

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THE INHIBITION OF RUSSELL'S VIPER VENOM BY CONGO RED

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CONGO RED can inhibit the conversion of fibrinogen to fibrin by thrombin[1] and the clotting of human plasma by the coagulase of the *Staphylococcus aureus*.[2] Russell's viper venom can clot recalcified plasma. The role of the Russell's viper venom in this process may be that of an enzyme, acting on some protein component of the serum to produce potent coagulant activity.[3] Since Congo red can inhibit the coagulation of fibrinogen by thrombin and by the coagulase of the *Staphylococcus aureus*, it seemed natural to learn whether the dye would prevent the clotting of recalcified human plasma by Russell's viper venom.

A mixture of a 0.01 per cent solution of Russell's viper venom, Stypven,* and a 1.0 per cent solution of anhydrous calcium chloride was made. A part of this mixture was added to human plasma and a 0.2 per cent solution of Congo red (Table I). The results showed a critical level of Congo red at which Russell's viper venom was inhibited from clotting recalcified human plasma (Table I).

TABLE I. THE RESULTS WITH A 0.2 PER CENT SOLUTION OF CONGO RED

NUMBER OF TEST TUBE	HUMAN PLASMA (ML.)	CONGO RED (ML.)	CONGO RED (MG.)	CONCENTRATION OF CONGO RED (PER CENT)	DISTILLED WATER (ML.)	STYPVEN AND CALCIUM CHLORIDE (ML.)	RESULT	TIME IN HOURS
1	0.2	0.0	0.0	0.00	1.4	0.4	+	2
2	0.2	0.1	0.2	0.01	1.3	0.4	+	2
3	0.2	0.2	0.4	0.02	1.2	0.4	–	6
4	0.2	0.3	0.6	0.03	1.1	0.4	–	6
5	0.2	0.4	0.8	0.04	1.0	0.4	–	6
6	0.2	0.5	1.0	0.05	0.9	0.4	–	6
7	0.2	0.6	1.2	0.06	0.8	0.4	–	6
8	0.2	0.7	1.4	0.07	0.7	0.4	–	6
9	0.2	0.8	1.6	0.08	0.6	0.4	–	6
10	0.2	0.9	1.8	0.09	0.5	0.4	–	6
11	0.2	1.0	2.0	0.10	0.4	0.4	–	6
12	0.2	1.1	2.2	0.11	0.3	0.4	–	6
13	0.2	1.2	2.4	0.12	0.2	0.4	–	6
14	0.2	1.2	2.4	0.12	0.6	0.0	–	6

\+ Clot present.
– Clot not present.

COMMENT

Congo red is an acid diazo dye with a molecular weight of 696.658. The manner in which Congo red acts in this process is not known. It is difficult to

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*The Stypven was supplied by Burroughs Wellcome & Co., (U.S.A.), Inc., Tuckahoe, N. Y.

assign specific toxicity to any of the constituents, any of the linkages, or the charge of the dye. Congo red competes successfully for reactive sites on the fibrinogen, however, with the coagulating substance. The union of Congo red with fibrinogen is apparently on a stoichiometric basis.

SUMMARY

Congo red had the ability to inhibit the formation of fibrin clots when Russell's viper venom was added to human plasma. An apparent stoichiometric relationship was present between the Congo red and the fibrinogen in the human plasma.

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ORIGIN OF FIBROBLASTS IN EXPERIMENTAL HEALING WOUNDS: AUTORADIOGRAPHIC STUDIES USING TRITIATED THYMIDINE

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THE origin of fibroblasts has been a subject of some controversy, for although it is generally accepted that fibroblasts arise from fibroblasts and from connective tissue cells,[14] whether they can also arise from lymphocytes,[3] macrophages,[12, 13] histiocytes,[7] endothelial cells,[2] fat cells,[8] and other cellular elements has been disputed.

A favorite manner of studying the origin of fibroblasts has been to observe their appearance in experimental healing wounds, often following various experimental procedures.[10] Methods to supplement histologic observations have been needed, however, and these have been sought in the biochemical, histochemical, and physical measurement fields.[6] Recently, the development of tritiated thymidine, with its advantages in detecting new cell formation through the preparation of autoradiographs[9, 11] suggested that this would be a supplemental technique. Tritium, or hydrogen^{-3}, offers particular advantages in autoradiographic work because of the low energy of its beta particle, 18.5 Kev., which is the lowest of that of any of the artificial isotopes. This permits identification in autoradiographs of individual cells and portions of cells that have taken up tritium, since the emitted particles travel an average distance in tissue of only 2 microns, with a maximum of 7 microns. Tritium has a half-life of 12.5 years so that once incorporated into a substance, it may be available for study for a long period of time. Thymidine, a pyrimidine component of desoxyribonucleic acid (DNA), is of especial use because it occurs only in DNA,[15] which in turn is present only in the nucleus of a cell.[5] Since the DNA of a cell nucleus is considered to be stable except when the nucleus synthesizes additional DNA in preparation for division, injection of tritiated thymidine followed by preparation and study of autoradiographs provides a unique method of detecting cells that are synthesizing DNA. This is of particular value when it is noted that such cells and cell nuclei are in general histiologically indistinguishable from other cells. Studies to date indicate that injected tritiated thymidine is available to cells for the synthesis of DNA for only a brief time, of the order of 15 to 30 minutes after an injection.[12]

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This method was applied to the problem of the origin of the fibroblast as follows. It is known that after production of wounds in the skin of rats, fibroblasts are formed as part of the healing process. If tritiated thymidine is injected into an animal at various times after the production of wounds, the tritiated thymidine should be taken up by cells that have been stimulated to form new cells, including those that will become fibroblasts. When these have divided to form new cells, the new cells will still carry the tritiated thymidine, generally in quantities of one-half that originally present. If biopsies of wounds are made at spaced intervals after an injection in a given animal, it should be possible to find cells in progressive stages of DNA synthesis, division, and formation of new cell types. The problem is somewhat complicated by the fact that several different cell types, and cells whose fate is ultimately quite different, may all be synthesizing DNA at approximately the same time. In the present study this proved to be the case, but two features helped to overcome this disadvantage. The first was that, at different stages in the healing of the wounds, different cell types were active in DNA synthesis, although there was some overlap. The second was that the use of tritium in autoradiographic work also permits histologic examination of individual cells, and the migration and fate of cells to which attention was called in autoradiographs by their synthesis of DNA could be followed and studied.

MATERIALS AND METHODS

Twenty rats* weighing 160 to 180 grams, aged 43 days, were used. These were male littermates from 5 litters. During the morning of one day, 4 widely separate surgical incisions were made in the skin of the back of each animal after the fur had been clipped with scissors, but not shaved over selected areas. With a scalpel, a single incision was made in each of the four areas, extending for a length of approximately 1 inch and in depth down to, but not through, the fascia overlying the deep muscles of the back. The wounds were then closed with two interrupted silk sutures in each wound. At periods of zero time up to 6 days after the wounds had been made, the rats were given a single intraperitoneal injection of tritiated thymidine,† 1.0 microcurie per gram of body weight. Biopsies of the wounds were made at varying times from 2 hours up to 14 days after the wounds and the injections. The biopsy tissue was partially sectioned at right angles to the wound three times to insure adequate fixation and fixed in 10 per cent neutral buffered formalin for 24 hours. Following washing, dehydration and clearing, imbedding in paraffin, and sectioning at 6 to 8 microns, standard histologic preparations stained with hematoxylin and eosin and autoradiographs, by a stripping film technique,[4] were made. Our use of this method has been described in detail elsewhere[11]; one change was introduced, however. Ordinarily, histologic preparations consist of 2 to 6 microtome cuts of tissue in strips of paraffin mounted serially on a glass slide. This technique was changed by mounting alternate microtome cuts of tissue on each

*Sprague-Dawley strain. Purchased from Charles River Breeding Laboratory, Cambridge, Mass.

†Schwarz Laboratories, Mount Vernon, N. Y. Specific activity 1.9 curies per millimole.

of two slides. One completed slide of a pair was used for the hematoxylin and eosin preparation and the other for autoradiographs. In this way, the stained autoradiographic tissue could be compared with the alternate cut of tissue stained with hematoxylin and eosin. The same cell could often be identified in both sections, and questions regarding the morphologic identity of individual cells in the autoradiographs could be better studied in the histologic preparations. Approximately 16 slide preparations were made from each wound, 8 for autoradiographs, and 8 for histologic preparations.

When thus prepared, film was placed over unstained tissue, dried in moving cool air, and sealed in light-tight boxes for 4 weeks. At the end of this time, films were developed in Kodak-19 developer for 7 minutes, washed briefly, placed in Kodak acid fixer for 10 minutes, washed in running cool tap water for 20 to 30 minutes, stained with hematoxylin, and mounted in polyvinylpyrrolidone (PVP),* which allowed permanent mounting from 80 per cent ethyl alcohol.

RESULTS

In the regions of the wounds, cell nuclei took up the tritiated thymidine in considerable quantities, a phenomenon that is referred to as "labeling" in autoradiographs. Labeled lymphocytes were present in the incisions and in adjacent dermis and subcutaneous tissues; judging from their lack of relationship to blood vessels and lymphatic channels, lymphocytes appeared to have taken up the labeled thymidine while in the skin as well as while in lymph nodes. Other mononuclear cells, identified as macrophages and histiocytes, were noted 2 to 4 hours after lymphocytes appeared and their nuclei were also heavily labeled. Approximately 48 to 72 hours after the incisions had been made, the numbers of labeled lymphocytes and other mononuclear cells reached a peak, and thereafter were present in decreasing quantities. Beginning at approximately 48 hours after the creation of the wounds, and with peak activity from 72 to 120 hours, tritium labeling was prominent in the nuclei of fixed undifferentiated connective tissue cells along the adventitia of veins and arteries, in connective tissue cells along hair follicles, and in connective tissue cells along injured muscle fibers, all underlying or adjacent to wound areas. Fibroblasts were first noted in proximity to these cells, as illustrated in Figs. 1 to 4, and they began to appear at a time when tritium labeling in lymphocytes and other mononuclear elements of the blood was decreasing. Once formed, at approximately 72 hours, fibroblasts migrated into wound sites, subsequently dividing to form additional fibroblasts. Fat cells and mononuclear cells normally present in the collagenous portion of the dermis did not take part in proliferative activity, as evidenced by the fact that at no time did they show tritium labeling. The same was true of polymorphonuclear leukocytes, since for practical purposes they also did not exhibit tritium labeling at any of the stages after the creation of the wounds.

*Antara Chemicals, New York 14, N. Y.

Fig. 1. Fig. 2.

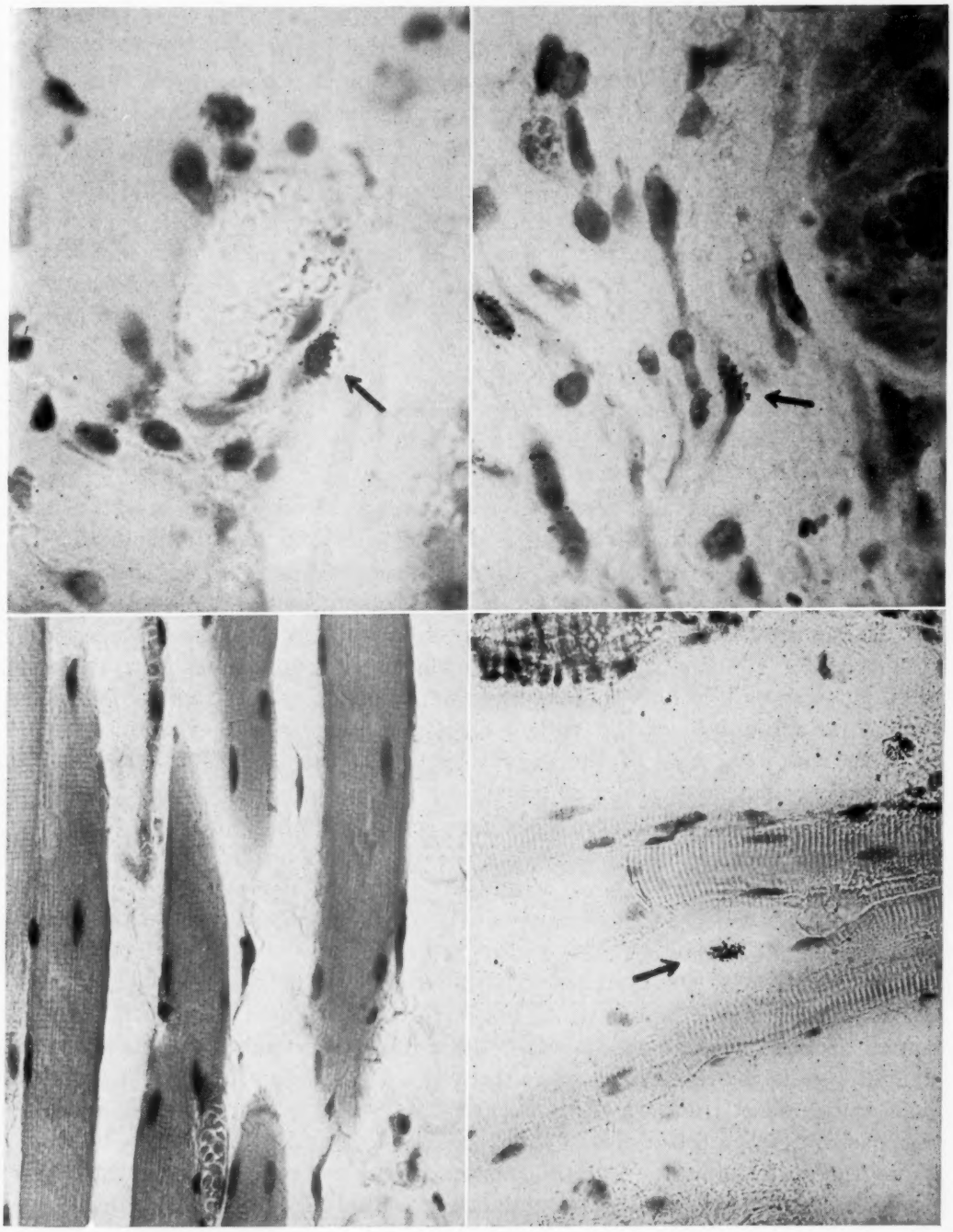

Fig. 3. Fig. 4.

Fig. 1.—Autoradiograph of vein beneath healing incised skin wound. Note adjacent tritium-labeled fibroblast. (Hematoxylin. ×800; reduced ⅘.)

Fig. 2.—Autoradiograph of hair follicle adjacent to wound. Note tritium-labeled fibroblasts. (Hematoxylin. ×800; reduced ⅘.)

Fig. 3.—Histologic section of injured muscle adjacent to healing skin wound. Note connective tissue cells, or fibroblasts, "peeling off" from muscle fibers. (Hematoxylin and eosin. ×800; reduced ⅘.)

Fig. 4.—Autoradiograph of injured muscle adjacent to an incised wound. Note labeled connective tissue cell, or fibroblast. (Hematoxylin. ×800; reduced ⅘.)

Other anatomic structures related to the healing of the wounds, such as epidermis at the stage when bridging of the incision was occurring and endothelial cells of capillaries in the subdermal tissue, also showed considerable tritium labeling.

COMMENT

When the present experiments were begun, it was expected that lymphocytes and macrophages and perhaps several other types of cells would give rise to fibroblasts in the course of the healing of wounds. The results were somewhat surprising, therefore, for it was concluded that lymphocytes, monocytes, and histiocytes played no part in the formation of fibroblasts. Fibroblasts were often found in proximity to histiocytes and to lymphocytes in the base and at the edges of healing wounds where fibroblasts were proliferating, and it is likely that this, together with the observation that lymphocytes, macrophages, and histiocytes frequently showed slightly elongated or tapering cytoplasmic processes, thereby resembling fibroblasts to a slight degree, has led some workers to conclude that fibroblasts arise from these cells.

Histologists agree that along the adventitia of blood vessels, as well as surrounding many structures such as muscle bundles and hair follicles, there is a system of undifferentiated connective tissue cells that probably bear an intimate relation, in these regions, to vascular channels.[14] These are the cells that in the present study gave rise to fibroblasts. It was not possible to determine whether along muscle fibers these cells were separate from sarcolemmal cells, but adjacent to hair follicles they were quite distinct from the epithelial cells of the follicles by virtue of their elongated nuclei, and they were separated from the epithelial cells of the follicle by a thin rim of eosinophilic staining, apparently collagenous, acellular tissue.

In the work of others, fibroblasts have consistently been observed to migrate into wounds from the periphery, despite an abundance of lymphocytes and macrophages in the centers of wounds.[16] This has not appeared to be consistent with the concept that fibroblasts arise from lymphocytes and macrophages, but rather that fibroblasts arise from fixed connective tissue cells and migrate into a wound site. In the present studies, once fibroblasts formed from connective tissue cells, they in turn gave rise to additional fibroblasts. In the course of these further subdivisions, the tritiated thymidine was passed on to daughter cells in decreasing concentrations. Eventually, in what appeared to be a rather short time, usually less than 3 days, the labeled thymidine had become so diluted by cell divisions that labeled cells could not be detected by autoradiographic techniques. For this reason, it was not sufficiently informative to give an animal with healing wounds an injection of tritiated thymidine, and then defer biopsy and autoradiographic examination until the wounds were completely healed. Instead, autoradiographic studies were most informative when carried out at intervals of not more than 3 to 5 days after a single injection of the labeled thymidine, before this became too diluted for detection.

Tissue culture studies have often been cited as evidence that various cellular elements of the blood are capable of differentiating into fibroblasts.[1, 3, 12, 13] In

such studies, cells such as the lymphocyte have been observed in vitro to develop elongated cytoplasmic processes. Practically every type of cell, however, when maintained for a few days under similar conditions, has developed such processes, and grown to resemble fibroblasts. Apparently, the factor of surface phenomena influencing the morphologic appearance of cells grown in vitro has not been taken into account in tissue culture studies, nor have the so-called fibroblasts that have been derived from blood cells been shown to elaborate collagen, as a functional test of their having differentiated into true fibroblasts. A point in the present work against tissue culture results was the finding that polymorphonuclear leukocytes in the wounds were not labeled in autoradiographs for at least 4 days after an injection of tritiated thymidine, and then to a very minimal degree. This probably indicated that, once formed, polymorphonuclear leukocytes were not capable of further proliferation and they were also not capable of differentiation into other cell types. Nevertheless, the polymorphonuclear leukocyte has been one of the many cells that in tissue culture has assumed elongated cytoplasmic processes and morphologically has resembled fibroblasts.[1]

SUMMARY AND CONCLUSIONS

A study has been made of the origin of fibroblasts in healing incised wounds in rat skin. Histologic and autoradiographic techniques were employed following periodic injections of tritiated thymidine, in order to detect cells utilizing the thymidine to synthesize DNA in preparation for division, and as a means of subsequently detecting these labeled cells. Fibroblasts arose from fixed connective tissue cells adjacent to the adventitia of arteries and veins, around hair follicles, and lining muscle fibers, in the subdermal tissue beneath and adjacent to wounds. Fibroblasts were not observed to arise from lymphocytes, macrophages, histiocytes, polymorphonuclear leukocytes, fat cells, endothelial cells, or fixed cells commonly observed in the collagenous portion of the dermis. Labeled fibroblasts were seen in autoradiographs in greatest numbers when tritiated thymidine was given 3 to 5 days after the wounds had been made, while at earlier periods lymphocytes showed peak labeling. It is concluded that in rat skin fibroblasts arise only from fixed connective tissue cells, and subsequently undergo division to form additional fibroblasts.

Technical preparations were made by Helen Cadegan, Lorraine Martin, Jane Donelan, and Richard Lewis.

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THE EFFECT OF ISOINDOLINE ON SURVIVAL OF RATS SUBJECTED TO ACUTE THERMAL BURN

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THE investigation of burn shock has left many questions unanswered. The significance and the mode of action of neural and toxic factors in shock are still inadequately known. Of particular interest in this area is the finding of Simonart and his Belgian co-workers.[20] According to them, various proteins, upon being heated to above 80° C., acquire toxic properties for frogs and rabbits. Thus it appeared worthwhile to investigate the effect of various temperatures on burns of equal area. Simultaneously an attempt was made to supplement Laver's[8] observation of the protective action of two ganglion blockers by the use of an additional long-acting blocking agent.

Isoindoline*—4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)—represents a departure from the symmetrical configuration around the methylene chain, as in the methonium series, and possesses a halogenated aromatic heterocyclic substituent,[15] thus resulting in a longer-acting and more potent drug. When tested in the nictitating membrane preparation of the cat 0.05 mg. per kilogram produced the same 50 per cent ganglion blockade as 0.32 mg. per kilogram of hexamethonium; however, the intravenous LD_{50} in rats was similar.[15]

Thus it seemed logical to test the efficacy of this agent in prolonging the life expectancy of rats subjected to a hot water burn. Moreover, an attempt was made to determine the influence of relatively small changes in the temperature of the burn—85° C., 90° C., 95° C.—of treated and control rats.

METHOD

The procedure utilized in the experiments was a slight modification of the method described by McCarthy.[12] Two hundred apparently healthy light-brown rats, of the Russian Mura strain, varying in weight from 150 to 250 grams, were used. It may be added that these rats were found to be particularly resistant. The animals were kept in wire cages at constant room temperatures (23° to 22° C.) and fed a diet of dried pellets and water, ad libitum.

Anesthesia was induced by placing the animal in a 3 L. bell jar through which a well-dispersed oxygen-ether mixture was passed for 4 minutes. In order to facilitate handling throughout the burning process, the rat was held around the neck by a piece of short rubber tubing attached to a pincette; the hindlegs and tail were grasped together in one hand. A scald was produced by immersing the back of the rat in a water bath at a constant temperature of 85° C.,

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*Ecolid is made by Ciba Ltd., Basle, Switzerland.

90° C., or 95° C. for exactly 35 seconds. Special precautions were taken to prevent burning of the neck or extremities. Excess water was removed after immersion by rolling the animals on an absorbent cotton towel. Sodium chloride, 0.2 c.c. of a 0.9 per cent solution (control), or 0.2 c.c. of a solution of 1 mg. in 1 c.c. of Isoindoline was injected into one of their lateral tail veins. The amount of Isoindoline was well in the intravenous LD_{50} range for the rat (28 mg. per kilogram).[15] The animals were selected at random for treatment or to serve as controls.

Following burning, the animals were replaced in a 3 L. glass jar with a 3 cm. aperture at the bottom to allow for the removal of urine and fecal material, and kept at room temperature. No food or water was given after the burn.

Survival was checked at half-hour intervals for the first 12 hours, then at 2-hour intervals. Rats that lived longer than 24 hours were sacrificed. All our animals were dissected within 2 hours after death. The burned skin was excised, cut in half, and a new incision perpendicular to the dissection was made in order to compensate for the curvature when determining the area of the burn. The perimeter of the burned area was traced into cellophane and determined by planimetry. The proportion of burned to unburned surface areas was expressed in percentages, according to the formula $S = KW\ 0.6$ ($K = 12.54$) as formulated by Lee[9] for the white rat.

The mean survival in the two extreme weight groups (150 to 200 and 200 to 250 Gm.) were compared in all our three temperature classes and differences were found insignificant. In the 85° C. class t was 2.1; in the 90° C. class t equaled 1.95; and 0.55 was the t for our 95° C. group. The two extremes in burned surfaces, that is 23 to 26 per cent and 28 to 31 per cent, were also compared in our three temperature sets. The difference in mean survival time was found not to be significant, t being 0.3, 1.0, and 0.65 in the 85° C., 90° C. classes. These findings verified those of Laver.[8]

All our results include animals weighing 150 to 250 Gm. with a burn of 27 ± 4 per cent surface area.

RESULTS

Table I summarizes our findings. Analysis of these results supports a hypothesis that intravenous injection of 0.2 mg. of Isoindoline immediately post burn significantly prolongs the mean survival time in all three temperature ranges investigated. As can be seen, t was 11, 22, and 11 in the 85° C., 90° C., and 95° C. groups, respectively, p being less than 0.001 in all three categories.

TABLE I. SUMMARY OF FINDINGS

BURN TEMPERATURE		NUMBER	MEAN AREA BURNED (PER CENT)	MEAN WEIGHT (GRAMS)	MEAN SURVIVAL TIME (MINUTES)	t	p
85° C.	Treated	27	27.1 ± 1.3	215 ± 49	1,289 ± 186	11	0.001
	Control	26	27.3 ± 2.1	208 ± 35	1,189 ± 367		
90° C.	Treated	29	27.1 ± 2.1	197 ± 27	1,018 ± 276	22	0.001
	Control	21	28.0 ± 3.5	191 ± 30	792 ± 437		
95° C.	Treated	12	28.1 ± 2.6	205 ± 51	386 ± 175	11	0.001
	Control	14	27.6 ± 1.6	207 ± 38	309 ± 161		

Fig. 1 shows more vividly how these results compare. The survival time of our control groups was found significantly altered; depending on the temperature used, p was less than 0.001.

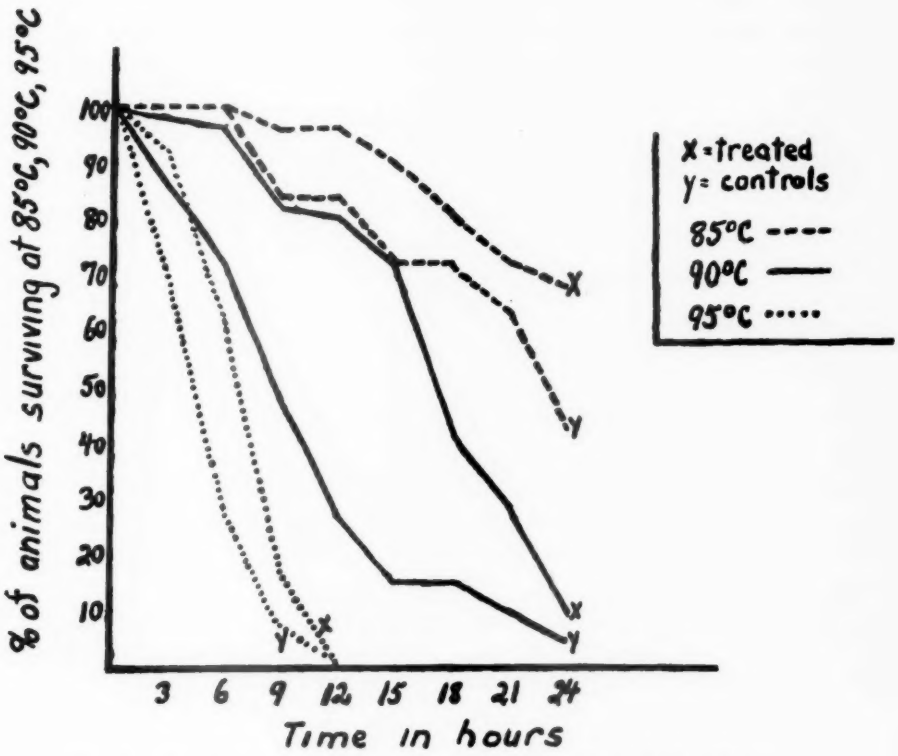

Fig. 1.—Comparing survival time of treated and control animals.

DISCUSSION

The mean survival time of our controls is significantly influenced by relatively minor temperature differences. Six hours after burning all the animals of the 85° C. group were alive as compared to only 28 per cent of our 95° C. group. This could be due to a gradual increase in fluid loss with increasing burn temperature. Although we did not measure for fluid loss in our experiments, we could see no obvious difference in swelling of the excised burned areas at the various temperatures. Indeed it is well known that edema formation decreases with increasing temperature and duration of burn, because of local circulatory arrest. Prinzmetal[17] showed that rats the legs of which were dipped in a water bath of 100° C. for 2 to 3 minutes, exuded 2 per cent of their body weight, while other rats burned at 75° C. for 10 seconds lost 5 per cent of their body weight. Edema was far more profound in the latter case. Nevertheless, there was a shorter survival time in the more severely burned group. It may, therefore be concluded that toxic and/or nervous influences could be important factors in causing decreased survival time.

The investigations of van Canegham,[3] Simonart,[20] and Allgöwer and Mégevand[2] point to the fact that proteins heated to above 80° C. may induce toxic reactions. These last investigators[2] injected heated blood coagula intraperitoneally in

rabbits. Thirty animals received 50 to 100 c.c. of blood heated to 100° for one hour. Almost 50 per cent of these died within 48 hours without excessive peritoneal exudation. Intraperitoneal injection of blood heated for one hour at 80° C. caused no death in 11 rabbits during the same period.

The significant difference in survival time between our rats burned at 95° C. and 85° C. thus is apparently not due to increased fluid loss at the former burn temperature. This too seems to suggest that some toxic and/or nervous factors play a part at the higher temperature.

By using the composite survival times of the first 24 hours we established a significant life prolongation time in those rats (150 to 250 Gm.) intravenously treated with 0.2 mg. Isoindoline. Ross and Herczeg[18] in a small series of animals noted that a critical dose range of ganglion blockers including Isoindoline was required to produce a certain degree of protection in pretreated rats submitted to drum trauma. One to 5.0 mg. per kilogram of Isoindoline was found to be the optimum dosage, with higher and lower dose levels causing a decrease in the protective action, but this dose was injected intraperitoneally. Although the danger of puncturing the intestine or viscera is slight, there is irregularity in absorption, particularly if the circulation is impaired, as may be the case in trauma. Also, the virtue of using the 24-hour period as in the case of these authors has never been shown to possess particularly advantage or validity. We can see in Table I that, in the 90° C. group, 80 per cent of the controls were dead 12 hours post burn as compared to 26 per cent of the treated animals. Thus if none had survival 24 hours it would be impossible to detect any subtle differences.

The prolongation of mean survival time by ganglion-blocking agents seems to suggest their attenuating effect on nervous shock. Blocking of autonomic ganglia decreases the sympathetic and parasympathetic discharge. Isoindoline has been shown empirically to have a greater blocking action on the sympathetic than the parasympathetic nervous systems.[11, 13, 15, 19] It has to be kept in mind, however, that blocking agents also cause hemodynamic changes, thus reducing exudation, that is, fluid loss. The data of Phemister and Laestar[14] and Wang and Overman[21] lend support to the view that both excessive vasoconstrictor tone due to an increased discharge of nociceptive stimuli from the burned area and fluid loss into the affected area are moderated by the hypotensive drug.

Using Isoindoline, we were able to confirm Laver's findings that treatment with a ganglion-blocking agent post burn had a significant effect on survival time. In most other shock procedures, pretreatment is the only effective method. Administration of the drug immediately after burning may be somewhat equated to pretreatment in other shock forms, since the burn gradually initiates the process (fluid loss, nervous excitation, and possibly toxin resorption), which in the other forms of shock takes place almost at once.

The findings that treatment after burn trauma is effective could have some practical value, since the application of a ganglion-blocking agent may delay the critical survival time, which is in great part ultimately determined by the rate of fluid loss.

SUMMARY

1. Increasing the temperature of a hot water burn in rats from 85° C. to 95° C. resulted in a significant decrease of mean survival time.

2. Treatment with Isoindoline (0.2 mg. per rat) immediately after burning resulted in a significant increase of mean survival time in all temperature ranges tested, the effect of the blocking agent being most obvious at 90° C.

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THE EFFECT ON THE KIDNEYS OF CROSS-CLAMPING THE ABDOMINAL AORTA DISTAL TO THE RENAL ARTERIES

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ONE of the recognized complications of the excision of abdominal aortic aneurysms has been oliguria in the postoperative period. This may progress to frank anuria. As a result of this, a significant number of deaths from renal failure has been reported. The histologic examination of the kidneys in the patients who died from this cause has shown distal tubular damage. This damage has varied from hydropic degeneration to complete necrosis.

Therefore, to investigate this problem of renal damage, a series of experiments on dogs was devised, with the object: (1) of producing renal damage by cross-clamping the aorta distal to the renal arteries; (2) of studying the effects of this cross-clamping on the secretion of urine; and (3) of evaluating possible means of preventing this histologic damage to the kidneys and the functional depression resulting therefrom.

METHOD

Unselected healthy mongrel dogs, of average body weight of 8 kilograms, were anesthetized with pentobarbital. The abdominal aorta was exposed, dissected free for a short distance, and occluded by means of a Pott's multitoothed vascular clamp placed just distal to the renal arteries (Fig. 1). A preliminary renal biopsy was taken and if this showed evidence of pre-existing disease, the animal from which the biopsy was taken was excluded from further experiments. In an initial group of 5 dogs the aorta was occluded for 2 hours and when the animals were sacrificed renal tubular damage was regularly seen. The distal convoluted tubule was the most affected part of the nephron, but the proximal tubule was also the site of a lesser degree of damage. Four hours of aorta clamping likewise produced tubular damage. The effect of 2 hours of aorta clamping was not greatly different from that produced by the longer period; therefore, in all subsequent experiments the aorta was cross-clamped for 2 hours only. Groups of dogs subjected to the clamping procedure were sacrificed at intervals of from one to 7 days after operation in order to determine the optimal time for sacrifice of the animals. The pathologic changes in the kidneys were best seen 7 days after operation when the degenerative and some regenerative changes were obvious in the affected renal tubules. All subsequent experiments,

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therefore, utilized 2 hours of aorta clamping and the dog was sacrificed on the seventh day. These initial experiments showed that clamping of the abdominal aorta of the dog regularly produced renal tubular damage (Fig. 2). The biopsy specimens taken prior to application of the clamp were normal on histologic examination.

The mechanisms whereby this damage was produced were next considered. Ischemia of the hindlimbs of the animal during the time of aorta clamping appeared complete. The peripheral pulses in the hindlimbs disappeared during this time and no measurable blood pressure distal to the clamp was detectable while the clamp was in position. No trauma to large muscle masses occurred during this experiment and this fact, plus absence of histologic findings consistent with those of the crush syndrome, suggested that the crush syndrome mechanism was not involved.

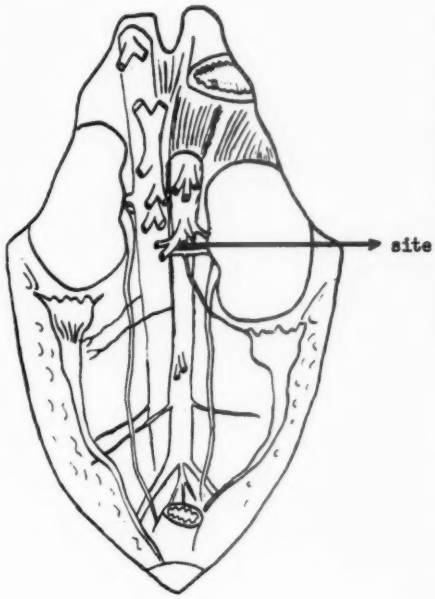


Fig. 1.

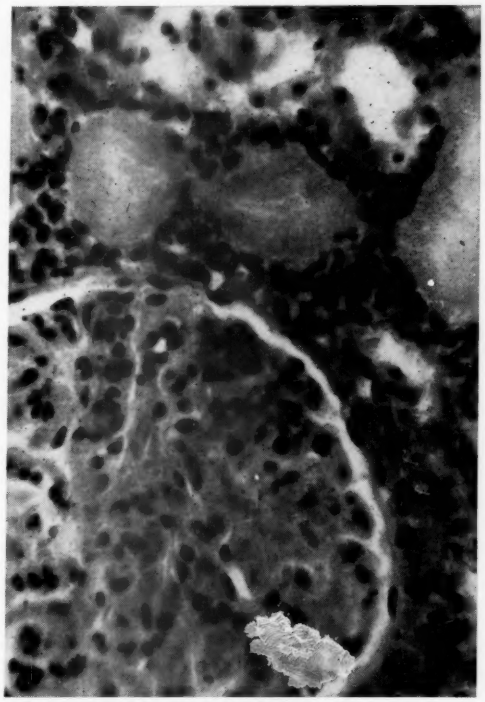
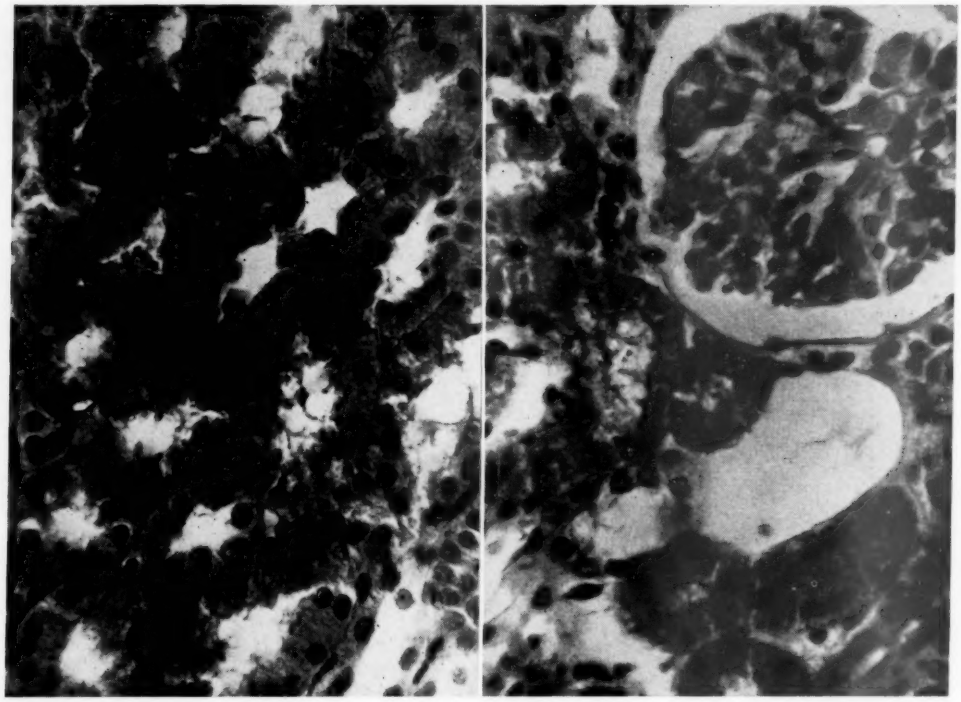


Fig. 2.

Fig. 1.—Showing site of cross-clamping of aorta just below renal arteries.
Fig. 2.—Histologic section of kidney of a dog whose aorta had been cross-clamped for 2 hours and subsequently sacrificed 7 days later. This shows gross tubular necrosis.

Renal artery embolism from the aorta proximal to the clamp was next considered as a possible cause. Atherosclerosis was not demonstrable in the aorta of any of the animals used and no histologic evidence of embolism was found. Therefore, this explanation was excluded. Direct measurements of blood pressure in the renal arteries during the period of aorta clamping showed no deviation from control values. Thus a further theoretical cause of damage, that of a "water-hammer" effect, was excluded. The renal tubular changes produced were therefore considered to be ischemic in nature and the mechanism was

thought to be one of arteriolar constriction caused by the aortic clamp. Mechanical trauma to the aorta caused by repeated closure and release of the clamp did not produce renal tubular damage. If the aorta was infiltrated with Xylocaine prior to clamping, renal damage was produced as before. It appeared, therefore, that ischemia of the part distal to the clamp was necessary to cause renal tubular damage.



A. *B.*

Fig. 3.—*A*, Histologic section of kidney of a dog whose aorta had been cross-clamped 7 days before. This was the left kidney which had been protected by infiltrating 2 per cent Xylocaine into the left renal pedicle. No tubular necrosis seen. *B*, Same dog as in Fig. 3, *A*, but this is the right kidney which had not been protected with Xylocaine. Note tubular necrosis.

The effects of renal artery denervation and the use of the ganglion-blocking agent Arfonad to protect the kidneys from the deleterious effects of aorta clamping, were reported in 1957 by Powers, Boba, and Stein.[1] In view of this report, in the next five experiments the renal pedicle on one side was infiltrated with local anesthetic. Two per cent Xylocaine without epinephrine was used and 4 c.c. of this solution were injected under the adventitia of the renal artery immediately prior to the application of the aortic clamp. The contralateral kidney served as a control. The aorta was occluded for 2 hours and the dogs were sacrificed 7 days later. Histologic sections from these animals showed the usual tubular degenerative changes on the control side (Fig. 3, *B*), while the changes on the side infiltrated with Xylocaine were much less evident (Fig. 3, *A*).

This observation agreed with that of Power and his associates, who noted minimal histologic changes if the renal artery was denervated prior to clamping

of the aorta. The use of local anesthetic appeared to achieve the same result. Five further experiments were conducted in which a ganglion-blocking agent was employed during the period of aorta clamping. Arfonad was utilized for this purpose. This drug is readily controlled and its hypotensive and ganglion-blocking effects do not persist for long after its administration is stopped. A dilute solution of Arfonad was given by intravenous drip at an appropriate rate to lower the systolic blood pressure to 70 to 80 mm. Hg. The abdominal aorta was occluded by clamp for 2 hours, the Arfonad drip discontinued, and the animal sacrificed 7 days later. The examination of histologic sections from the kidneys of these animals showed normal appearances in 4 of the 5 dogs and the fifth one showed only minimal changes (Fig. 4).

Fig. 4.—Histologic section of kidney of dog the aorta of which had been cross-clamped 7 days before, but which had been protected by an Arfonad intravenous drip. Tubular necrosis much less, compared with Fig. 2.

The effects of clamping the abdominal aorta on the output of urine were next determined. An intravenous infusion of 500 ml. of 5 per cent dextrose and water was given over a period of 30 minutes in order to provoke a large output of urine. In this group of 5 animals the urine flow from each kidney was measured. In some dogs the ureters were exteriorized and in others the bladder was divided into two pouches, each pouch draining one ureter. The flow of the urine was identical in the control experiments. One dog, which was the exception, was discarded from the experiment and later shown to have only one normal kidney, the other kidney being rudimentary and very small.

In the same animals, after the recovery period, the aorta was exposed and clamped. Local anesthetic was infiltrated into one renal pedicle and the

intravenous infusion once more given. The renal flow from the control side was usually suppressed, while the flow from the infiltrated side was profuse (Fig. 5). In one dog the output from the infiltrated side was 90 times that of the control, but more commonly a volume four times as great as that of the control was obtained. Similar effects were still obvious several days later, when a further infusion was given (Fig. 6).

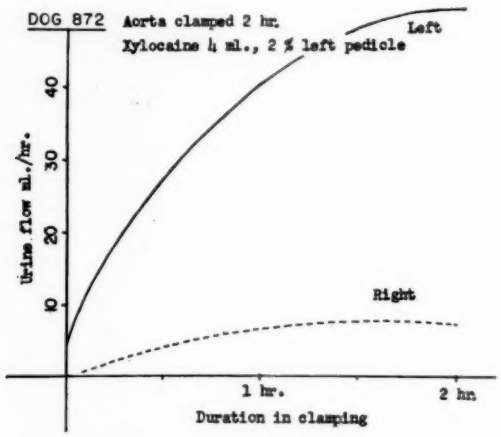


Fig. 5.—The effect of infiltrating the left kidney pedicle with 2 per cent Xylocaine on the urine flow in response to a 500 ml. infusion of glucose and distilled water. This experiment was performed at the time of the cross-clamping.

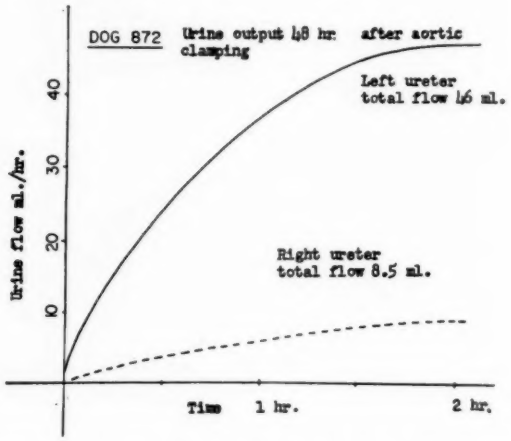


Fig. 6.—The same dog an in Fig. 5, but a further infusion of 500 ml. of glucose and distilled water given 48 hours later. The same type of response obtained as at the time of cross-clamping. Oliguria of right kidney still present.

In this group of experiments the noninfiltrated kidney served as a control for the opposite one. It was further confirmed in other dogs in which neither kidney was infiltrated that oliguria usually resulted from clamping the abdominal aorta. (An occasional animal showed a diuresis when the aorta was clamped, but this was the exception.)

The effects of Arfonad were next investigated in animals prepared so that the urine output could be measured from individual kidneys. Five such experiments were conducted. The first experiment consisted of giving the dog 500 ml. of infusion in 30 minutes, as before. The urine output was measured

over the subsequent 2 hours. After a recovery period of a few days, a similar infusion was repeated, but in addition Arfonad was given to lower the systolic pressure to 75 to 80 mm. Hg. The urine output was again measured for 2 hours. After a further recovery period, another 500 ml. infusion was given and Arfonad was once more given, and the aorta was clamped for 2 hours. Urine outputs were again measured.

The results were as follows: The urine output in the second series of experiments in which Arfonad was employed was lower than that of the controls in each case. When the aorta was clamped and Arfonad given, however, the urine output in 4 of the 5 dogs exceeded that in the corresponding control experiment, in one case being five times as great (Fig. 7). These experiments showed that the use of local anesthetic to the renal pedicle or of ganglion blockade with Arfonad during clamping of the abdominal aorta could reduce the degree of tubular damage which otherwise resulted. Likewise the depression of urinary output which is usually associated with aorta clamping was largely prevented by either agent.

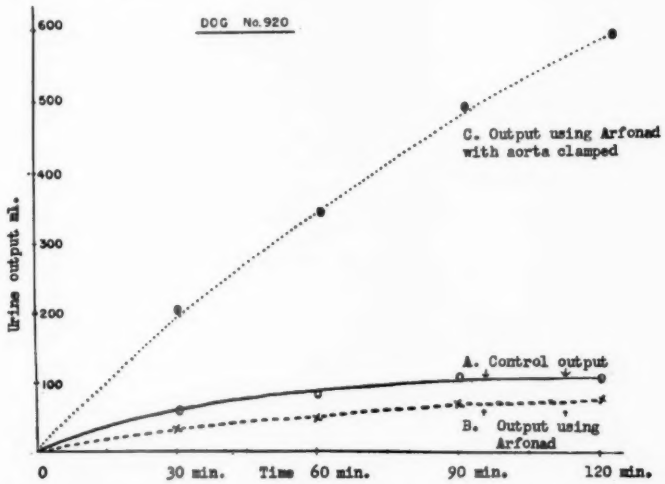


Fig. 7.—Effect of Arfonad on the diuretic response to an infusion of 500 ml. of glucose and distilled water, with and without cross-clamping of the aorta.

Direct measurements of renal blood flow during clamping of the abdominal aorta showed no reduction below control values. If ischemia of the kidney was the cause of renal tubular damage it appeared that the renal blood flow was being shunted away from the renal cortex during the time of aorta clamping.

In order to investigate this point further, India ink was injected directly into the renal arteries to outline the vessels of the kidney. The control dogs showed an even distribution of the dye throughout the renal cortex. When injection was carried out after 2 hours of aorta clamping, the renal cortex contained very little injected material when sectioned at autopsy. It was further observed in these cases that the renal veins became intensely stained with the injection material within seconds of the commencement of renal artery injection, suggesting a large arteriovenous shunt within the kidney. This observation suggested that the renal blood flow was largely being shunted away from the renal cortex.[2]

The results of injecting India ink into the renal artery during aorta clamping in dogs, in which Arfonad or infiltration of the renal pedicle with Xylocaine had been used, demonstrated results identical with those seen in the control experiments, namely, the kidney was diffusely stained with India ink in a normal manner (Figs. 8 and 9). Therefore, these injection experiments appeared to confirm that cortical ischemia did occur during aorta clamping and could be prevented by the use of either Arfonad or of renal pedicle infiltration with Xylocaine.

Fig. 8.

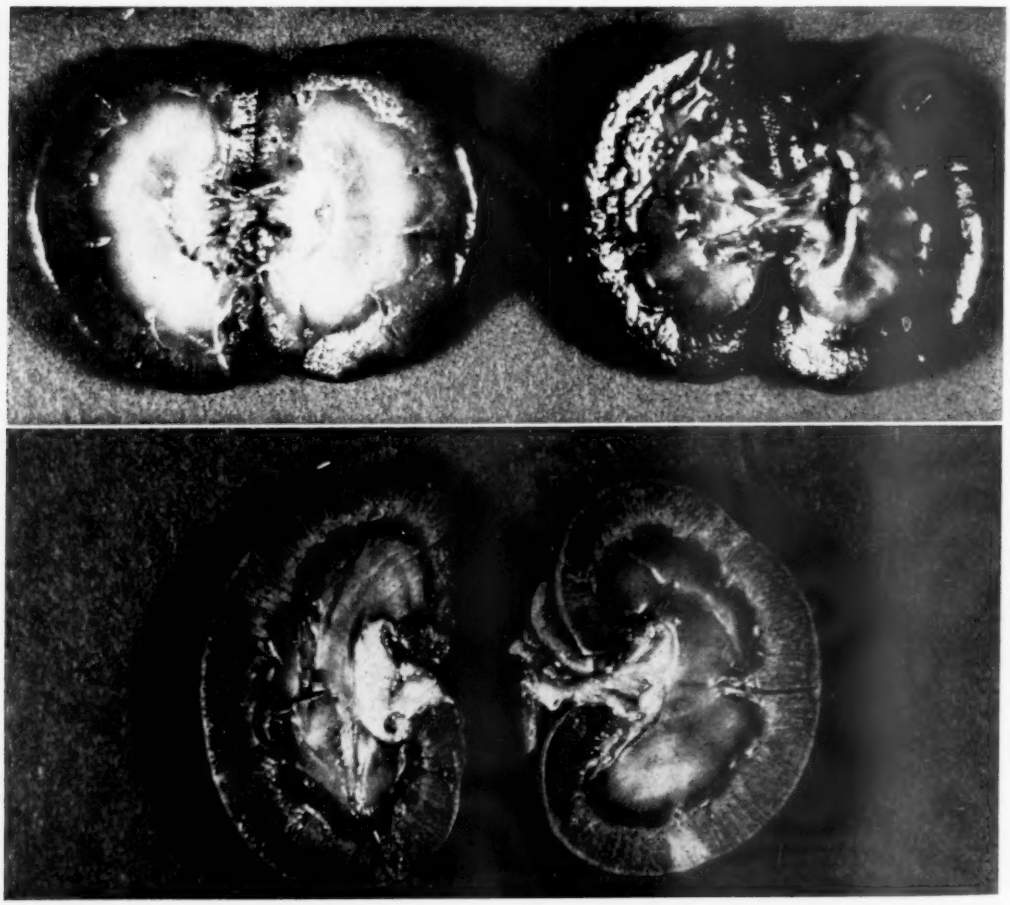


Fig. 9.

Fig. 8.—India ink injected into aorta above clamp; left kidney protected with 2 per cent Xylocaine. Right kidney unprotected and therefore showing little dye compared with left.

Fig. 9.—Two hours' clamping with Arfonad. India ink injected into aorta above clamp in a dog protected with Arfonad. Dye well diffused throughout both kidneys.

SUMMARY

These experiments (Table I) showed that:

1. Clamping of the abdominal aorta of a dog distal to the renal artery produced renal tubular damage and depression of urinary output.

2. The use of ganglion blockade or of infiltration of the renal pedicles with Xylocaine during clamping of the abdominal aorta largely prevented the tubular damage and depression of urinary output.

3. The use of infiltration of the renal pedicle with Xylocaine during the surgical removal of human abdominal aortic aneurysms has been employed by one of the authors (E. M. N.), and in these cases no postoperative depression of renal function has occurred.

TABLE I. SCHEME OF EXPERIMENTS ON CLAMPING THE ABDOMINAL AORTA OF THE DOG

NUMBERS OF DOGS	DURATION OF CLAMPING	POSTOPERATIVE DAY SACRIFICED	PATHOLOGIC FINDINGS
7	2 hours	1 to 7	Tubule damage best seen at 7 days
5	2 hours	7	Tubular damage
5	4 hours	7	Tubular damage
5	Nil, dissection only	7	Negligible
5	2 hours, Xylocaine left pedicle	7	Slight changes right and left
5	2 hours, Arfonad used	7	Slight changes

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A BLOOD FLOWMETER FOR EXTRACORPOREAL SURGERY

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IN RECENT years, cardiac surgery with the aid of extracorporeal circulation has demonstrated a need for a reliable blood flowmeter. A flowmeter should have the following qualities:

1. Simplicity in use, cleaning, and sterilizing.
2. Instant and prolonged accuracy.
3. No undesirable side effects such as interference with the pump, alteration of blood flow, or production of hemolysis.
4. Independence of viscosity, temperature, and changes in circulatory resistance.

The two methods of measuring blood flow in the extracorporeal circuit which have been employed are the use of the "venous" reservoir as a flowmeter or calibration of the pumps and estimating the flow from the revolution per minute quotient.

Both of these methods are inaccurate and may have serious disadvantages. They indicate normal or even increased flow when the blood passing through the system is seriously impeded or, because of some technical failure, such as clotting or suction-collapse of the plastic tubes, there is no flow at all. Another disadvantage is that, despite the time-robbing "calibrating" procedure before every surgical intervention, the "calibrated" output of the pumps is highly influenced by other factors, such as circulatory resistance of the patient, autoclaving of the tubing, etc.

In the past years several attempts have been made to design a reliable flowmeter, but none of these complicated and expensive instruments became popular in surgical practice. During the past 3 years, we have experimented with different types of flowmeters. In our experience the instrument which most closely approximates the ideal is the orifice-plate flowmeter.

The orifice-plate flowmeter uses the pressure differential caused by a constriction in the fluid conduit to infer the rate of flow. The primary element is the orifice plate itself; the secondary element is the pressure difference measuring and recording device. The basic principle of such meters was set forth by the Italian, Venturi, in 1797, who after much experimentation stated that fluids under pressure gain velocity and lose pressure head when passing

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through a stricture. This principle was elaborated in detail and expressed as one of the basic laws of hydrodynamics by the Swiss scientist, Bernouilli.

The steady flow of general energy equation between points *1* and *2* may be written in the following manner:

$$Z_1 + U_1 + P_1v_1 + V_1^2 + Q + W = Z_2 + U_2 + P_2v_2 + \frac{V_2^2}{2g}$$

in which:
V_1 V_2 = velocity of fluid at points *1* and *2*
Z_1 Z_2 = elevation between points *1* and *2*
U_1 U_2 = internal energy of fluid at points *1* and *2*
v_1 v_2 = specific volume of fluid at points *1* and *2*
Q = net heat transfer between points *1* and *2*
W = net amount of work performed between points *1* and *2*

In most of the cases, as in the present case, the *Z*, *Q*, *U*, and *W* terms may cancel, and the equation may be written in the following form:

$$P_1v_1 + \frac{V_1^2}{2g} = P_2v_2 + \frac{V_2^2}{2g}.$$

Replacing the specific volume *V* by its reciprocal, specific weight γ, and expressing $V_1 = V_2\ D_2^4/D_1^4$ for conduits of circular cross-section *D*, the equation will be:

$$V_2 = \frac{1}{\left(1 - \frac{D_2^4}{D_1^4}\right)^{1/2}} \sqrt{2g\left(\frac{P_1 - P_2}{\gamma}\right)}$$

where the $\frac{1}{\left(1 - \frac{D_2^4}{D_1^4}\right)^{1/2}}$ expression is known as the velocity approach factor and may be represented by the letter *M:*

$$V_2 = M \sqrt{2g\left(\frac{P_1 - P_2}{\gamma}\right)}$$

The volumetric rate of flow is equal to the area of the fluid stream *A* multiplied by the average fluid velocity *V:*

$$F = AV = AM \sqrt{2g\left(\frac{P_1 - P_2}{\gamma}\right)}$$

Because for a given fluid and flowmeter the factors *A*, *M*, and γ are constant *C*, the flow can be expressed by the difference of pressure between the points *1* and *2* of the meter:

$$F = C\ (P - P_2)$$

The *C* constants may be calculated or gained empirically.

The orifice-plate flowmeter used routinely in our open heart operations is made of stainless steel, silicone coated. The instrument is provided with safety shaft connectors for the plastic tubing on either end and has Luer Lok pressure taps on either side of the orifice plate. The plate itself is made of Teflon and is changeable. The flowmeter weighs less than 200 Gm. and is only 3 inches long. The gauge is easy to clean and needs no autoclaving (Fig. 1).

The differential pressure between the two taps is measured with a standard Statham SP pressure transducer, then calculated and recorded with an Electronics in Medicine Multichannel Oscillograph.

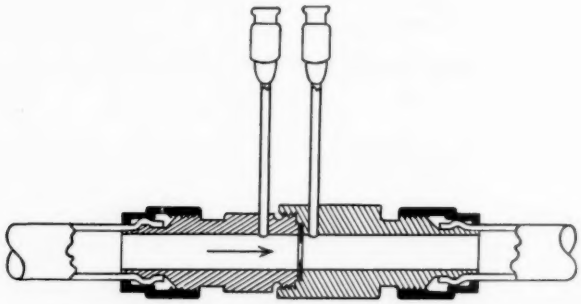

Fig. 1.—Schematic diagram of the flowmeter.

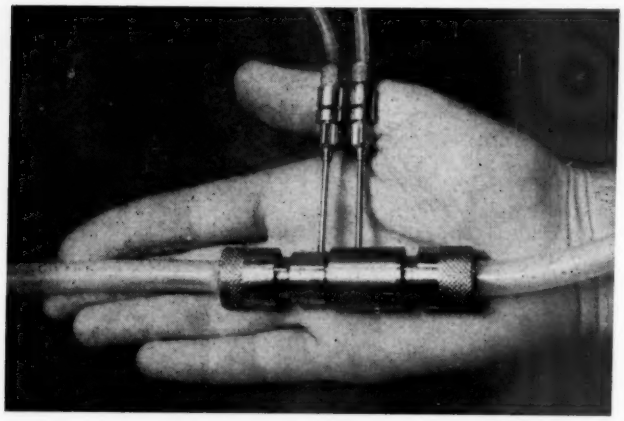

Fig. 2.—The orifice-plate flowmeter.

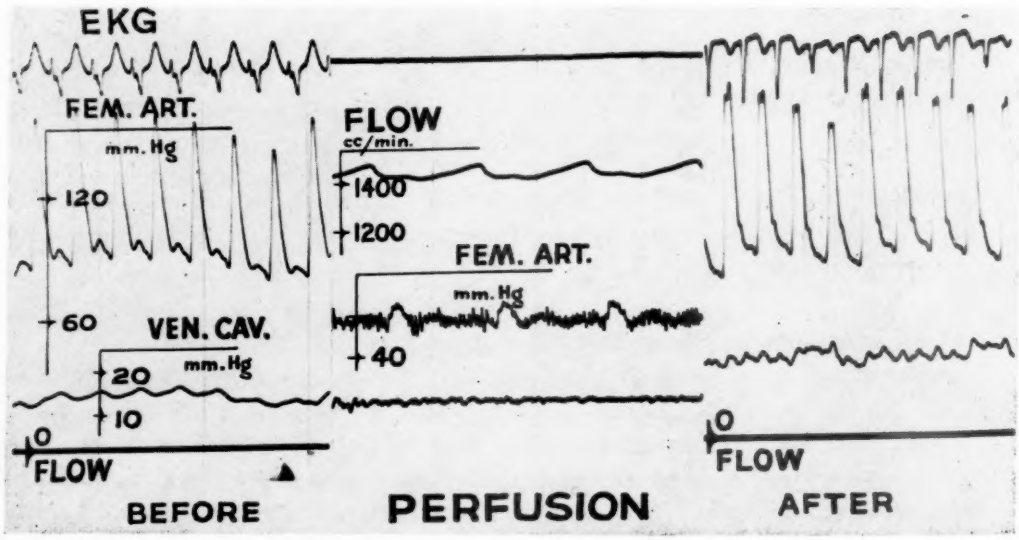

Fig. 3.—Simultaneous EKG, pressure and flow tracings before, under, and after cardiopulmonary bypass.

By using a highly sensitive electronic recording device we are able to use a relatively large orifice plate in our flowmeter. Thereby, undesirable side effects have been practically eliminated.

To study pumping efficiency and hemolysis, blood was circulated 1 hour through an extracorporeal system composed of a rotating disc oxygenator, twin De Bakey pumps, reservoir, filter, and bubble trap. Using an identical mixture of donor blood, the perfusion was repeated with the flowmeter in the system. Comparing the results of the experiments we found the free hemoglobin content of the plasma to be the same. The difference in the perfusion pressure and flow/r.p.m. ratio was < 0.03.

The free hemoglobin content of the plasma as an index is routinely determined in all of our patients after open heart surgery. With the flowmeter in the described extracorporeal system, following perfusions from 9 to 42 minutes, the free hemoglobin content of the plasma was < 130 mg. per 100 ml. This does not exceed the average values found in the literature.

The differential pressure principles and the orifice-plate flowmeter have proved to be highly efficient and accurate in our experimental and clinical work. An extra advantage of this meter is the simplicity of handling. Its introduction increased significantly the evaluation and safety of our open heart operations.

SUMMARY

The orifice-plate flowmeter has been described and its use in cardiopulmonary by-pass recommended. The instrument is simple, accurate, and easy to handle and sterilize.

THE EFFECT OF INTRA-ARTERIAL INJECTION OF RADIOPAQUE CONTRAST MEDIA ON CORONARY BLOOD FLOW

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RECENT interest in coronary arteriography as a diagnostic aid in the management of coronary insufficiency has stimulated investigation of the effects of the arterial injection of radiopaque contrast media. Successful clinical and experimental trials of this technique have suggested that it is relatively safe, although an exact understanding of the responses involved remains obscure.[1, 10] The present work concerns the experimental determination of coronary flow following direct injection of various media into the coronary circulation. The data obtained permit a quantitative analysis of the effect of these compounds on blood flow through the myocardial vascular bed.

METHODS

Eleven adult mongrel dogs (10 to 16.5 Kg.) were used. Intravenous pentobarbital (25 mg. per kilogram) was employed as an anesthetic, and respiration was maintained with oxygen through an endotracheal tube connected to a positive-pressure respirator. An incision was made in the left fourth intercostal space, the pericardium was opened, and the left main coronary artery was dissected at its origin from the aorta. Heparin (100 mg.) was administered intravenously. For measurement of coronary arterial flow, a recording rotameter[9] was then connected to a Gregg cannula secured in the left coronary artery, employing the left carotid artery as a source of blood as shown in Fig. 1.[6] The media studied were placed in graduated burettes and were perfused at the desired pressure by use of a mercury manometer attached to a constant pressure chamber. Arterial and injection pressures were constantly recorded by means of a strain gauge placed in the circuit (Fig. 1). A simultaneous electrocardiogram was also obtained. Normal saline, 76 per cent Renografin (sodium and methylglucamine 3, 5-diacetylamino-2, 4, 6-triiodobenzoate),† and 70 per cent Urokon (sodium 3-acetylamino-2, 4, 6-triiodobenzoate)‡ were employed as test materials. While coronary blood flow was briefly interrupted, measured quantities of these compounds were injected into the system at a pressure corresponding to the prevailing mean systemic arterial pressure.

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At the termination of the experiment, the heart was excised and the total heart weight, the total ventricular weight, and the combined left ventricular and septal weights were determined. All calculations of coronary flow and amounts of contrast media are presented as cubic centimeters per 100 grams of combined left ventricular and septal weight.

RESULTS

One hundred and thirty-three intracoronary injections of test materials were performed in 11 animals. The effects of normal saline, Renografin (76 per cent), and Urokon (70 per cent) were compared in 7 of these dogs.

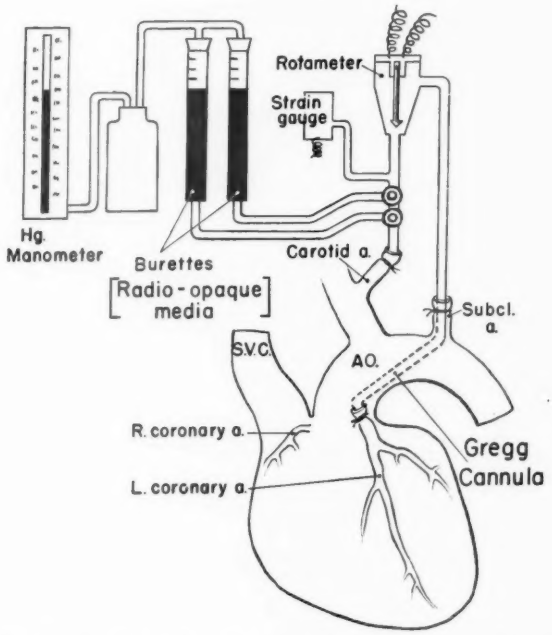

Fig. 1.—Diagrammatic illustration of method employed to determine coronary blood flow.

As a control observation, normal saline was injected in 50 instances. A graphic representation of the changes occurring in one animal following the injection of 6.4 c.c./100 Gm. of saline is shown in Fig. 2. The average changes found in 20 separate trials in which the amount of normal saline ranged from 6.8 to 8 c.c./100 Gm. is seen in Table I. In both instances, the typical alteration in coronary blood flow subsequent to injection consisted of an abrupt increase in flow reaching a peak within 7 to 12 seconds and followed by a return to control levels within a total period of 30 seconds. Individual variation occurred but the magnitude of flow deviation was directly related to the amount injected.

The effect of contrast media on coronary flow was studied following 83 injections of which 44 involved Renografin (76 per cent) and 39 Urokon (70 per cent). It may be seen that some difference existed in the average response obtained from similar quantities of these two materials, especially when large amounts were employed (Table I). Fig. 3 reveals a graphic representation of the alterations in coronary blood flow which followed three individual tests of

TABLE I. AVERAGE ALTERATION IN CORONARY BLOOD FLOW FOLLOWING INTRA-ARTERIAL INJECTION OF RADIOPAQUE MEDIA

SOLUTION	NUMBER OF TRIALS	QUANTITY INJECTED (C.C./100 GM.)	CONTROL FLOW (C.C./100 GM./MIN.)	INITIAL FLOW DECREASE (C.C./100 GM./MIN.)	SECONDARY FLOW INCREASE (C.C./100 GM./MIN.)	FINAL FLOW (C.C./100 GM./MIN.)	TIME FROM INJECTION TO FINAL FLOW (SECONDS)
Normal saline	20	6.8 to 8.0	95	0	59	96	28
76% Renografin	8	1.4 to 1.9	94	9	51.5	103	84
70% Urokon	6	1.4 to 1.9	70	3	36.5	71	85
76% Renografin	12	3.8 to 5.0	97	18	90	98	138
70% Urokon	9	3.8 to 4.8	87	20	67	90	204
76% Renografin	9	6.8 to 7.6	99	35	92	104	202
70% Urokon	4	6.8 to 7.6	130	97	24	99	241

varying quantities of contrast media. Each of these tests was felt to be a typical example of the group from which it was selected, with the average results of each of these groups presented for comparison in Table I. In each instance, the flow response subsequent to the instillation of radiopaque materials into the coronary artery assumed the form of a biphasic curve. The first component was a brief decrease in flow, followed by a secondary increase, and subsequently

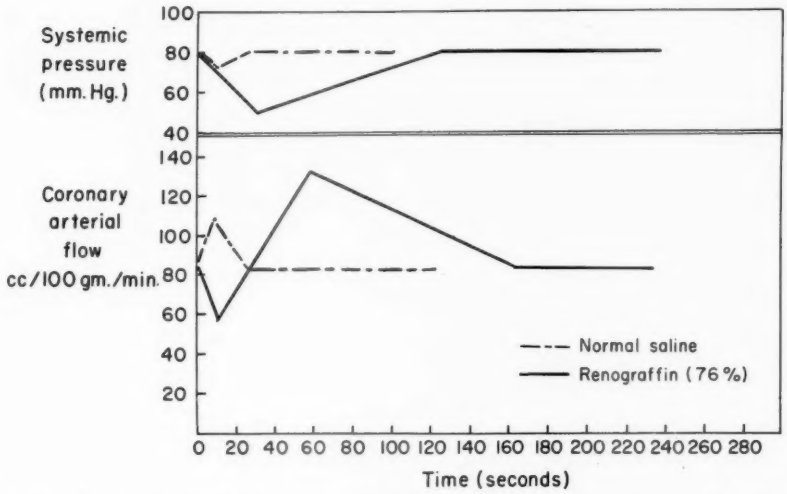

Fig. 2.—Comparison of intracoronary injection of normal saline and Renografin (76 per cent) on coronary blood flow.

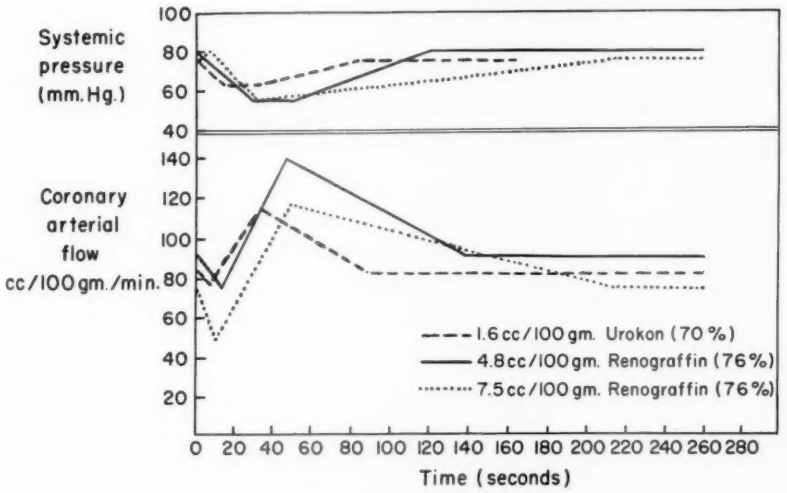

Fig. 3.—Comparison of effect of concentration of intracoronary radiopaque media on coronary blood flow.

a return to control levels. Similar unpublished observations have been made for other types of contrast media (Diodrast, Miokon, Hypaque).[7] The magnitude of these changes appeared to be related directly to the quantity of test material employed. Only with the highest amounts was some deviation noted, with the maximum augmentation in flow failing to reach the levels observed when smaller quantities had been used. It was felt that this phenomenon was

related to the lower levels of systemic blood pressure which followed single large injections of radiopaque materials. With the greatest quantities employed, the total time required for coronary flow to return to control levels was approximately 4 minutes.

Comparison of the results obtained with normal saline and contrast media in the same animal (Fig. 2) demonstrates that with saline the changes were fleeting and with maximal quantities occupied less than 30 seconds. The greatest increase in flow secondary to normal saline had usually occurred by the time the point of maximum decrease in flow, following the injection of radiopaque materials, had been reached. The period required for recovery from contrast media was 4 to 8 times longer than in the case of normal saline.

In general, the systemic blood pressure declined with decreases in coronary flow. Following a rise in coronary flow, the arterial blood pressure tended to return to control levels and in some instances exhibited a slight degree of rebound. In most instances, alterations in coronary blood flow appeared to precede any changes in systemic blood pressure, although the final recovery of the electrocardiogram and peripheral blood pressure usually occurred prior to the return of coronary flow to normal.

The injection of small quantities of test materials appeared to produce only minor changes in the electrocardiogram. With increased concentrations of radiopaque media, the alterations which were observed in some animals included elevation of the T-wave, appearance of extrasystoles, and varying degrees of atrioventricular block with bradycardia.

DISCUSSION

Intra-arterial injection of contrast media is known to result in alterations in arterial blood flow, although the exact form of this reaction has been debated. In 1933, Heathcote and Gardner demonstrated an augmentation of coronary flow in the isolated rabbit's heart following the instillation of Diodrast.[4] These authors also demonstrated dilation of the peripheral arteries of the dog following injection of this material. In 1942, Weatherall showed that Diodrast produced an increase in the force of contracture of the rabbit's heart.[11] This investigator concurred that this material also produced an increase in coronary blood flow, while in the peripheral arteries of the rabbit's ear it caused vasodilatation and in the arteries of the dog's leg led to a transient period of vasoconstriction followed by vasodilatation. There has been more recent evidence that the instillation of contrast media (including Diodrast, Urokon, sodium iodide, and Thorotrast) into the peripheral arteries of both dogs and human beings might produce a biphasic response, consisting first of a transient period of vasoconstriction followed by vasodilatation.[5, 8] In dilute solutions, only the phase of vasodilatation might be apparent. Foltz and associates[2] have demonstrated by direct visualization of the blood vessels of the cerebral cortex that intracarotid Diodrast causes considerable arteriolar spasm persisting for 1 to 2 minutes.

It is not surprising that the typical response noted in the present experiments following the intracoronary injection of contrast media appeared to be a brief period of coronary vasoconstriction followed by vasodilatation. As noted previously in the case of peripheral arteries, the phase of vasoconstriction tended to be obscured when smaller doses were employed.

The exact mechanism of the arterial response to the injection of contrast media has not been explained fully. That the initial decrease in coronary blood flow following the injection of radiopaque materials was absent in the case of normal saline would tend to eliminate anoxia as the only factor. Also, it is difficult to ascribe the alterations in coronary blood flow solely to changes in peripheral resistance, since the former invariably preceded any fluctuation in peripheral pressure. The hypertonicity and viscosity of these solutions must be important, but it is felt that, in addition, some component of the contrast media probably exerts a direct action on the coronary arteries.

Other investigators have demonstrated in the dog that the intracoronary injection of radiopaque materials might produce alterations in the electrocardiogram, varying from reversible T-wave changes and prolongations of the T-P interval to extrasystoles.[3] In the present study, high concentrations of contrast media tended to produce not only extrasystoles, but also degrees of reversible atrioventricular block varying from slight prolongation of conduction time to complete A-V dissociation. These quantities were considerably greater, however, than those employed in clinical studies.

With a knowledge of the effects of these contrast media on the heart, one might question their use in coronary arteriography. It should be noted, however, that the amounts required to produce severe cardiac abnormalities are much greater than one would expect to employ clinically. Assuming considerable mixing of blood and radiopaque materials with a normal coronary flow and average ventricular weight, the intra-aortic injection of 35 to 40 c.c. of 70 per cent Urokon should deliver to the coronary arteries amounts of contrast media comparable to the lowest dosages employed in this series. Moreover, the introduction of new radiopaque materials with diminished toxicity should lessen the reactions that have been observed.

SUMMARY

Coronary arterial blood flow has been determined by a direct recording rotameter and the effects of the injection of radiopaque media (Urokon and Renografin) have been studied. These compounds produce consistent changes when perfused into the myocardial vascular bed. This response is characterized by an immediate and brief reduction in flow followed by an increase and an ultimate return of flow to the control level. These changes appear to be the result of direct action on the coronary vascular bed with alterations in the systemic arterial pressure occurring as a secondary phenomenon. The changes noted are transient with rapid return of coronary flow to normal and do not appear to constitute a contraindication to the judicious use of contrast media in coronary arteriography.

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THE EFFECT OF INDUCED CHRONIC HYPERCHOLESTEROLEMIA ON CANINE THORACIC AORTIC TRANSPLANTS

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IN THE human aorta, atheromatous changes commence in the distal portion of the abdominal aorta, spread upward, and may be quite extensive while the thoracic aorta is still uninvolved.

In previous experiments, the development of atheromatous lesions under conditions of induced hypercholesterolemia was demonstrated in canine aortic grafts, placed just proximal to the trifurcation of the abdominal aorta.[2] In autografts, the changes were similar to those of the adjacent host aorta. In homografts, preserved in balanced saline solution or by lyophilization, the changes were more extensive than those of the host aorta.

The present study was undertaken to determine the effect of induced hypercholesterolemia on grafts placed in the canine thoracic aorta.

METHODS

Adult mongrel dogs were anesthetized with nembutal sodium intravenously. The left hemithorax was entered through an intercostal incision and the proximal segment of the descending aorta was mobilized, dividing one or two pairs of intercostal arteries. In one group, a segment of aorta about 2.5 cm. long was excised and then sewn back into place with running sutures of black silk, while in the second group a lyophilized homograft was used to replace the defect. Neither hypothermia nor shunts were used and the aortic occlusion time varied from 14 to 27 minutes. Following operation, thyroid ablation was accomplished by parenteral administration of radioactive iodine of one millicurie per kilogram of body weight. The animals were then placed on a diet of horse meat (70 per cent), Purina chow (25 per cent), and cholesterol (5 per cent). Serum cholesterol determinations, by the method of Abell and associates,[1] made prior to the administration of radioactive iodine, were repeated weekly until the experiment was terminated 3 to 13½ months later. At the conclusion of the experiment, the aorta was opened longitudinally to reveal the number and distribution of lesions, then the specimen was fixed in formalin and blocks of tissue were obtained for microscopic study from the graft and from portions of the host aorta. The blocks were imbedded in paraffin and, from each block, sections were cut and stained, respectively, with hematoxylin and eosin, Masson's trichrome, and Weigert's elastic tissue stains.

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RESULTS

Of the 30 animals subjected to operation, 10 failed to live long enough to be included. Of the 20 surviving animals, 9 had autografts and 11 homografts. Average serum cholesterol concentrations of 1,000 mg. per cent or higher were maintained in 3 of the animals with autografts and in 1 with a homograft (Figs. 1 and 2). As in previous studies, lipid changes were noted both in the grafts and the host vessels of these animals. The structural alterations in Dog 98 with an autograft in the thoracic aorta on the diet for 13½ months are shown in Fig. 3. The proximal suture line was 18 cm. from the trifurcation of the aorta and the graft was 2 cm. long. Minimal atheromatous plaques were observed along the clamp marks, suture lines, and in the graft. In the abdominal aorta, the plaques were more diffuse and of even distribution, particularly around the openings of the parietal branches. Microscopically (Fig. 4), lipid changes were minimal or slight. There were marked sclerotic and calcific alterations, particularly along the suture lines.

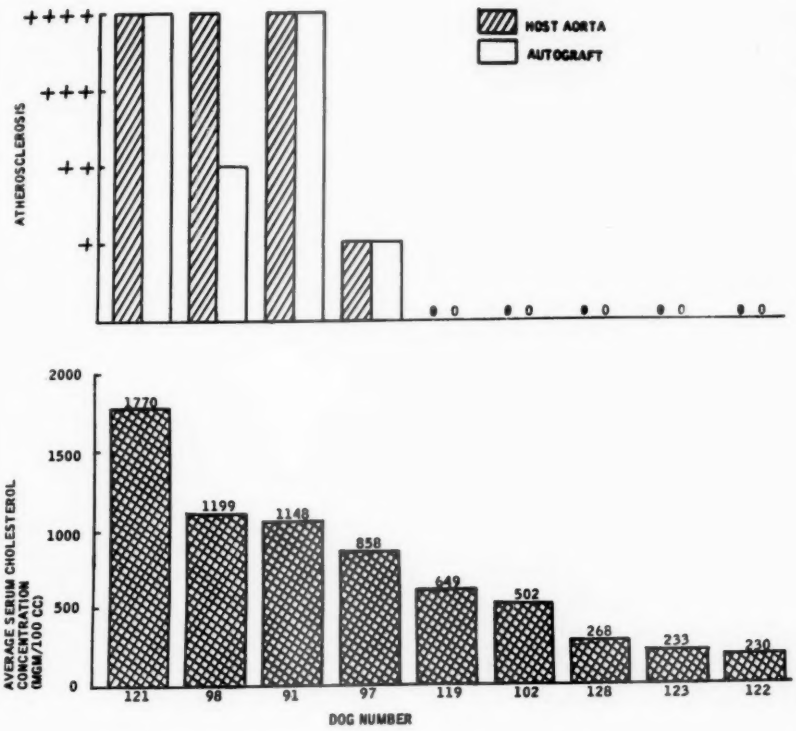
Average serum cholesterol concentrations of less than 1,000 mg. per cent were maintained in 6 animals with autografts and 10 with homografts. Atheromatous change occurred in only one dog with an autograft. This animal (Dog 97) was on the diet for 10 months. The proximal suture line was 13.5 cm. from the trifurcation and the graft was 1.5 cm. long. Atheromatous plaques involved both the graft and the host vessel only along the suture lines (Fig. 5). Microscopically, at the suture line the elastic fibers were disrupted with dense hyalinized, fibrous connective tissue which sealed the gap. In the overlying intima were numerous lipid-laden cells close to one another or between delicate fibrils (Fig. 6).

The homografts of 5 of 10 animals with average serum cholesterol concentrations less than 1,000 mg. per cent revealed lipid changes. These changes occurred only in the graft, the host vessel remaining uninvolved, except at the site of some clamp marks. Dog 247 was on the diet for 10 months. The graft was 2.5 cm. long and was located in the distal third of the thoracic aorta with the end 5 cm. proximal to the origin of the celiac artery. Sclerotic and atheromatous changes occurred only in the homograft and in the distal clamp mark (Fig. 7). Microscopically, in the graft, compact remains of the elastic fibers were irregularly interrupted. They were "sandwiched" between narrow bands of newly formed fibrous connective tissue on the intimal side and a wider band of dense, hyalinized, fibrous connective tissue on the adventitial side. Covering the intimal surface were lipid-laden large mononuclear cells in clusters or strands in a delicate fibrillar connective tissue (Fig. 8).

COMMENT

Previous experiments with homografts placed in the abdominal aorta suggested that the graft was more susceptible to the development of atheromatous change under conditions of induced hypercholesterolemia than was the host vessel. The number of animals used in those experiments, however, was not sufficient to allow definitive conclusions. It was also considered possible that the

Fig. 1.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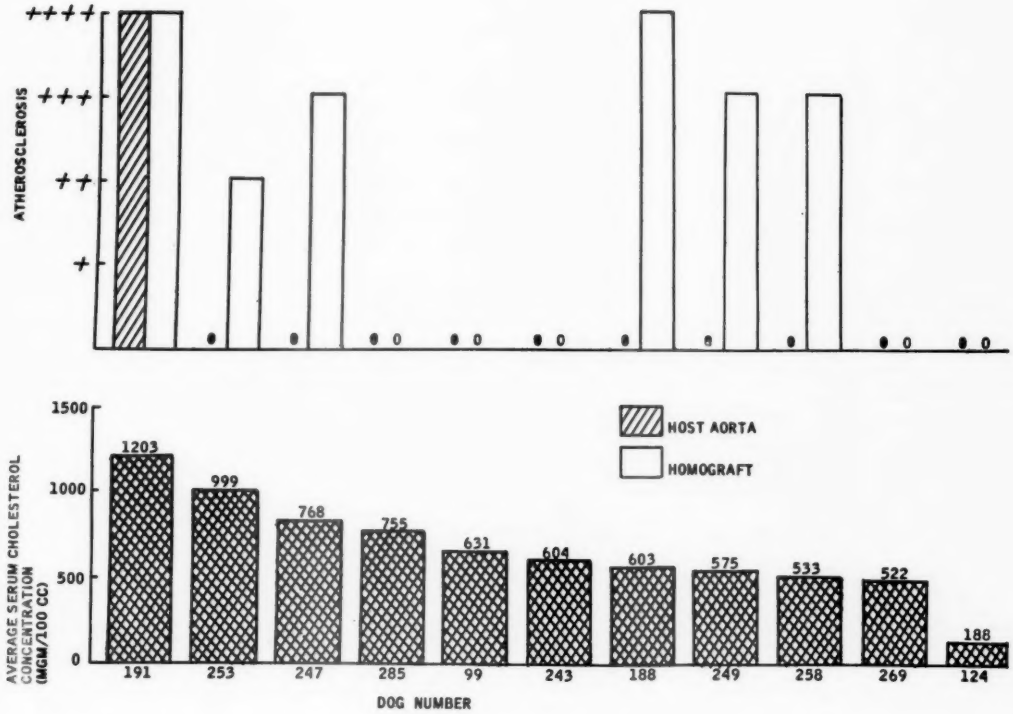
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Fig. 2.

Fig. 3.—Structural alterations in the aorta in Dog 98 with an autograft in the thoracic aorta, in which an average serum cholesterol concentration of 1,199 mg. per cent was maintained for 13½ months. There are minimal atheromatous plaques along the clamp marks, suture lines, and in the graft. The plaques are more diffuse in the abdominal aorta, mostly around the openings of the parietal branches.

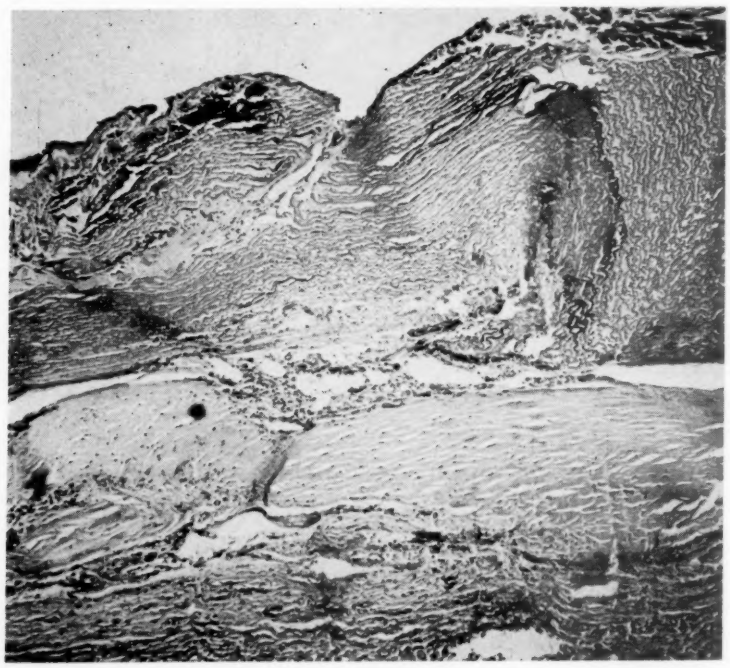

Fig. 4.—Microscopic appearance of the aorta in Fig. 3 along a suture line. Lipid changes are minimal. Sclerotic and calcific alterations are marked. (Hematoxylin and eosin; ×60.)

Fig. 5.—Structural alterations in the aorta in Dog 97 with an autograft in the thoracic aorta, in which an average serum cholesterol concentration of 858 mg. per cent was maintained for 10 months. The changes, atheromatous and sclerotic, of both the graft and the host vessel are limited to the suture lines.

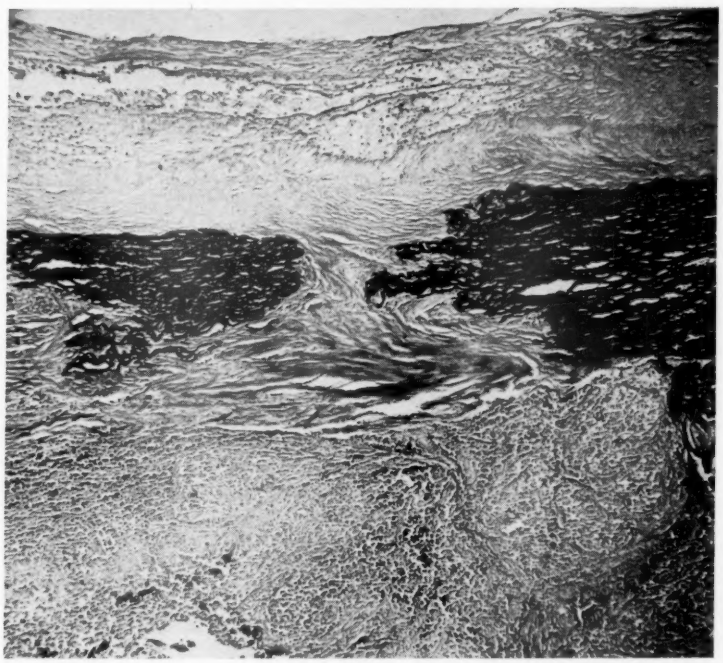

Fig. 6.—Microscopic appearance of the suture line in the aorta shown in Fig. 5. The elastic fibers are disrupted with dense, hyalinized, fibrous connective tissue sealing the gap. In the overlying intima, lipid-laden cells are numerous. (Weigert's elastic tissue stain; ×60.)

Fig. 7.—The thoracic aorta of Dog 247 with a homograft in the distal third, in which an average serum cholesterol concentration of 768 mg. per cent was maintained for 10 months. There are atheromatous and sclerotic changes only in the homograft and in the clamp mark near the distal suture line. There are none elsewhere.

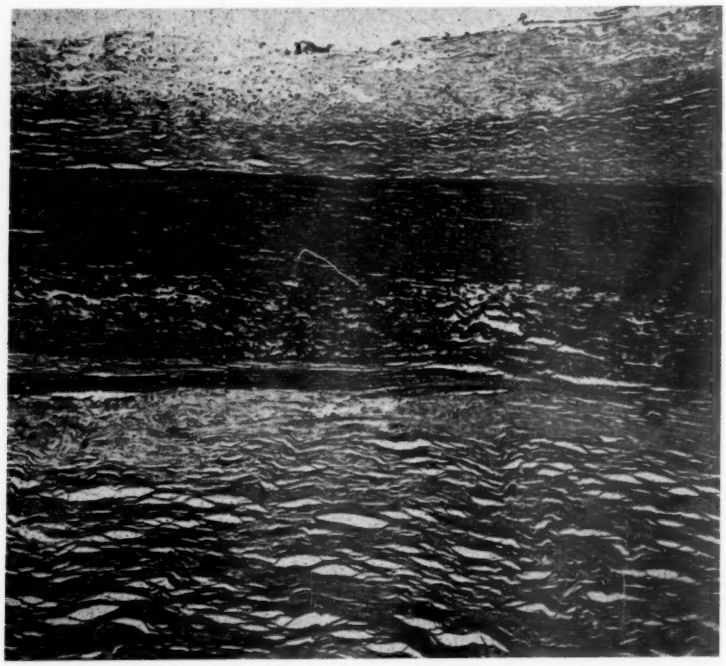

Fig. 8.—Microscopic appearance of the homograft in Fig. 7. In the graft, compact remains of the elastic fibers are irregularly interrupted. They are "sandwiched" between a narrow band of newly formed fibrous connective tissue on the intimal side and a wider band of dense, hyalinized, fibrous connective tissue on the adventitial side. Covering the intimal surface are lipid-laden large mononuclear cells in clusters or strands in a loose delicate connective tissue. (Weigert's elastic tissue stain; ×60.)

location in the aorta might be as important a factor as the presence of the graft itself. The present observations, that the changes also occur in grafts placed in the thoracic aorta in the absence of atheromatous change in the host vessel, support the concept that changes are related to the graft itself rather than to its location in the aorta.

It was noted that atheromatous plaques occurred adjacent to the suture line more often than elsewhere and, in some animals, the changes in the host vessel were mainly at the site of clamp marks. These findings are in line with the theory that local factors are of significance in the development of lipid changes. The studies of Haimovici and associates[3] indicate that fresh homografts behave in a manner similar to autografts. Preserved homografts were used in all of our experiments, and it is possible that the trauma incurred in the preservation of the homograft may have been more important in the development of lipid changes than the differences in the homograft and the host vessel. The alterations, occurring in the grafts and host vessels of these animals, that are of particular importance are the atheromatous lesions similar to those occurring in the human being with microscopically demonstrable foam cells, and the changes recorded here all pertain to this type of lesion. In this experiment, 4 of the 5 homografts with no lipid change had other retrogressive lesions grossly demonstrable, including calcification, and it is well known that homografts may develop this type of change even to the point of aneurysmal dilatation in the absence of hyperlipemia.

SUMMARY

This study is concerned with the effect of induced hypercholesterolemia on grafts placed in the canine thoracic aorta. Autografts or homografts were placed in the thoracic aorta of dogs. Then hypothyroidism was induced by administration of I^{131} and hypercholesterolemia by a high cholesterol diet that was maintained for 3 to 13½ months. The results indicate that lyophilized homografts are more susceptible to atheromatous change than the host vessel, irrespective of the site in the aorta, while fresh autografts are not.

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TRANSVENTRICULAR MITRAL VALVOTOMY

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NUMEROUS techniques of mitral valvotomy have been recommended and used during the years since Bailey,[1] Harken,[7] and Brock[2] reported their pioneering clinical efforts with mitral stenosis. The principle which was advocated in those early reports and which contributed to success of valvotomy has been followed in all subsequent modifications of a technical nature. Preservation of the integrity of the mitral leaflets is necessary in any such procedure if severe regurgitation is to be avoided. Thus, the primary objective of operation is separation of the fused valvar leaflets to achieve maximum increase in size of the orifice while maintaining the competence of the valve.

Techniques for mitral valvotomy, which have produced satisfactory results, include simple dissection or finger fracture, incision of the commissures with a variety of special valvotomes, and use of expanding dilators. Accurate assessment and comparison of results of each method of valvotomy would be difficult and, from a practical standpoint, impossible. In the majority of our own cases we have used an anterior fourth intercostal space approach to the left atrial appendage with transatrial finger fracture of the commissure.[3, 4] This technique has produced good or excellent functional results in approximately 70 per cent of patients. For approximately 20 per cent of patients, however, the nature of the pathologic process producing stenosis prevented satisfactory valvotomy. In our experience, sharp valvotomes have not provided the solution to the technical problem. Valvotomes may be difficult to manipulate inside of the heart and occasionally an accurate incision in the commissure results in serious mitral regurgitation. Calcification of the valve may prevent satisfactory valvotomy, regardless of the method employed. Moreover, forceful manipulations through the left atrium may dislodge thrombi which are frequently present, especially in advanced cases of mitral stenosis. For these reasons a more effective method of mitral valvotomy was desirable.

The technique of mitral valvotomy to be described has provided a satisfactory solution to some of these problems, and results have been improved significantly.

TECHNIQUE

The patient under general anesthesia is placed in a supine position on the operating table with the left shoulder elevated slightly on a folded towel. A curved submammary incision is made in the fifth intercostal space, anteriorly

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dividing the fifth costal cartilage lateral to the internal mammary vessels (Fig. 1, *a*). After inserting the self-retaining retractor, an incision is made in the pericardium parallel to the phrenic nerve, from the pulmonary artery above to the cardiac apex inferiorly. Traction sutures are placed on the edges of the pericardium to retract the lung posteriorly and elevate the heart and apex of the left ventricle in the operative field. Palpation of the atrial appendage may reveal the presence of thrombi. Care must be exercised to prevent dislodgment during subsequent maneuvers. A purse-string suture of 2-0 silk is placed around the appendage and attached to a modified Rumel cardiovascular tourniquet with ratchet (Fig. 1, *b*). If thrombosis is present in the appendage, the side of the left atrium may be used for direct entry to the mitral valve, using a purse-string suture applied in a similar manner.

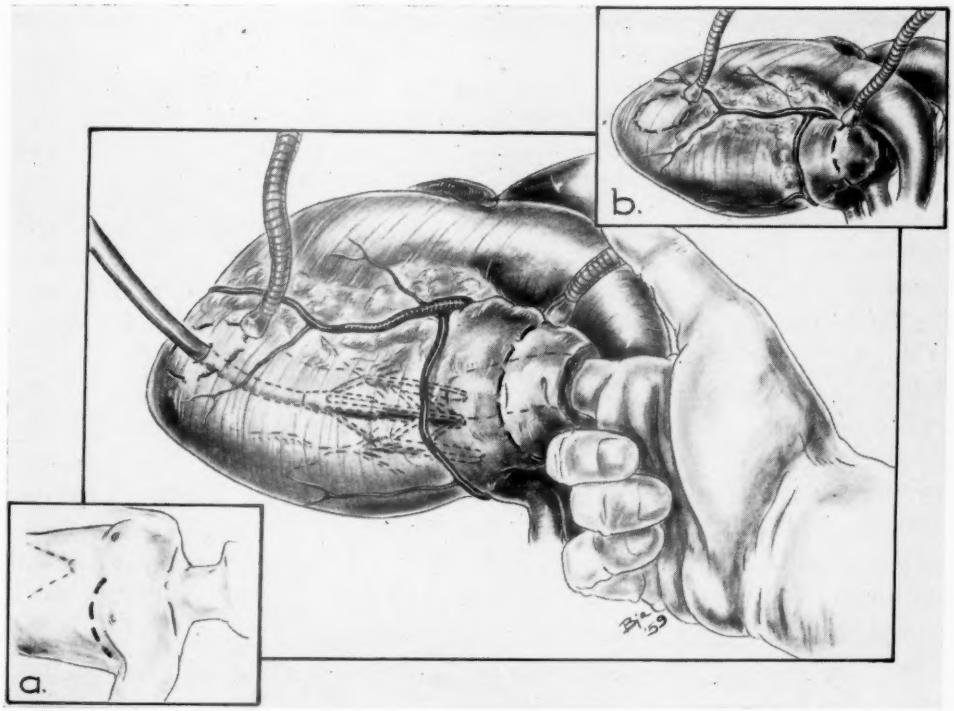

Fig. 1.—Drawing showing technique of transventricular mitral valvotomy using expanding two-bladed dilator. The instrument is guided into the mitral orifice and the extent of valvotomy is controlled by the palpating finger in the left atrium. Inset (*a*) shows the location of the submammary incision which enters the fifth intercostal space. Purse-string sutures and modified Rumel-Belmont tourniquets are placed on the left atrial appendage and the apex of the left ventricle.

The anterior surface of the left ventricle is identified after demonstrating the course of the anterior descending coronary artery. Near the apex of the left ventricle, a site, which has no large coronary vessels, is selected for insertion of a heavy purse-string suture, making a somewhat deep entry of the suture into the myocardium. This suture is likewise attached to a Rumel tourniquet with ratchet. During the intracardiac procedure, the tourniquets on the ventricle and atrial appendage are controlled by an assistant.

An incision is made through the atrial purse-string suture and, using the usual precautions to avoid dislodgment of thrombi, the surgeon introduces his right index finger. Assessment of the degree of stenosis and presence of mitral regurgitation is made. The extent and nature of calcific deposits are determined. An attempt is made to perform digital or finger fracture or to at least initiate the separation of fused leaflets. If stenosis persists, then the transventricular dilatation of the valve is performed.

After the exploration of the valve is completed and with the right index finger remaining in the left atrium, the surgeon makes a small stab wound into the area of myocardium surrounded by the ventricular purse-string suture. This incision may be only 15 mm. long and does not necessarily enter the ventricular chamber. A two-bladed expanding dilator is inserted into the stab wound and with a little pressure is introduced into the ventricular cavity with minimal blood loss. If the purse-string suture has been placed near the apex of the ventricle, the dilator easily enters the mitral orifice without becoming entangled in the papillary muscles or chordae tendineae (Fig. 1). The instrument must be introduced sufficiently far into the atrium and ventricle so that the expansion mechanism does not protrude through the ventriculotomy incision. The dilator is opened in the direction of the valve orifice, exerting pressure on each commissure. If dislodgment of atrial thrombi or embolization of calcific fragments from the mitral valve is anticipated, the common carotid arteries in the neck may be compressed briefly by the anesthetist to reduce the hazard of cerebral embolism. Isolation and control of the innominate and left common carotid artery at their origin from the aortic arch are not indicated and, in our experience, are unsafe. The valve is dilated widely up to 4.5 cm. and usually no mitral incompetence is produced. The dilator is closed and removed from the ventricle as the ventricular purse-string suture is tightened. The right index finger is withdrawn from the left atrium and the tourniquet around the atriotomy is closed and the ratchet set. The atriotomy is repaired by tying the purse-string suture, amputating the excess tissues, and placing several reinforcing sutures. The ventriculotomy incision may be repaired with two or three interrupted black silk sutures.

The pericardium is closed loosely and the thoracotomy is closed with chromic catgut sutures. An intercostal tube is inserted for subaqueous drainage.

A patient with recurrent mitral stenosis may be operated upon using the same left atrial and ventricular approach, but adhesions about the left atrial incision or the presence of atrial thrombosis may make a right-sided digital approach to the mitral valve more feasible. Under these circumstances, the incision used is a bilateral anterior thoracotomy into the left fifth intercostal space and into the right fourth space (Fig. 2, *a*). The sternum is transected with a Gigli saw and both internal mammary vessels are divided and ligated. The pericardium is opened transversely with a "T" extension anterior to the right phrenic nerve. A purse-string suture of 2-0 silk is placed at the interatrial groove in preparation for the right approach to the mitral valve as described by Neptune and Bailey[8] (Fig. 2, *b*). The ratchet-type Rumel tourniquet is

attached and an incision is made parallel to the groove and into the left atrium whereupon the surgeon inserts his left index finger. After assessment of the valvar function, the dilator is inserted through the previously placed purse-string suture in the apex of the left ventricle and guided into the mitral orifice (Fig. 2). The valvotomy is performed in a manner similar to that just described, using the bimanual technique. Usually valvotomy, even in the recurrent stenosis with a calcified valve, can be accomplished with the same degree of success as in the initial valvotomy. Upon completion of the valvotomy, the atriotomy and ventriculotomy incisions are repaired with interrupted sutures. The pericardium is closed loosely with interrupted silk sutures and the thoracotomy is repaired with bilateral intercostal subaqueous drains after placing stainless steel sutures in the divided sternum.

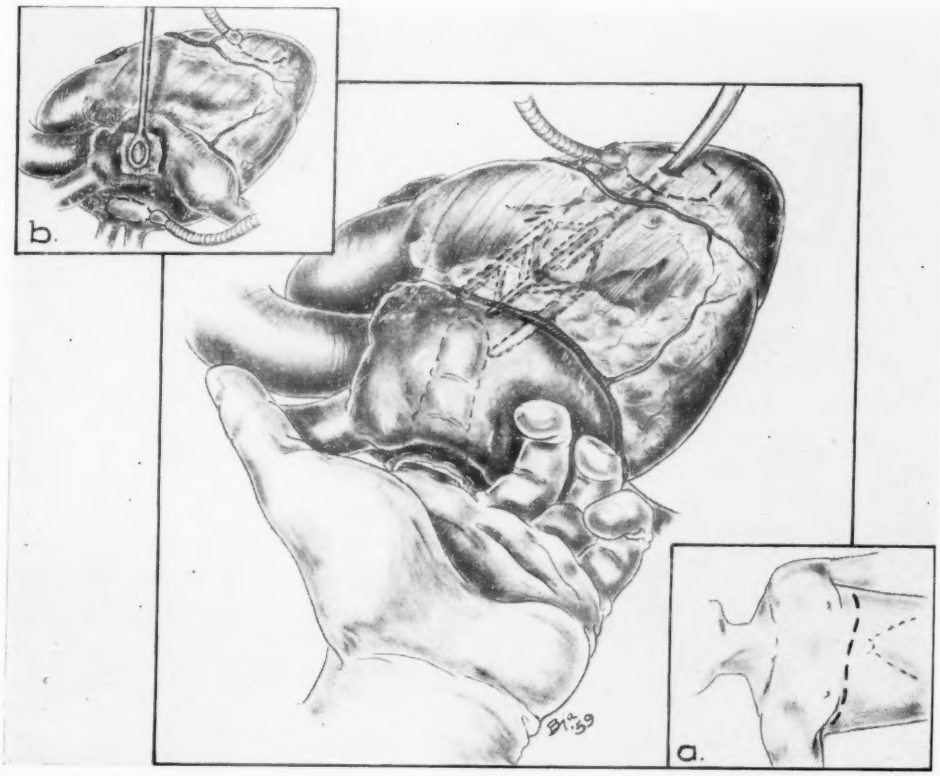

Fig. 2.—Drawing showing technique of transventricular mitral valvotomy using combined left and right approach. A bilateral anterior thoracotomy incision is made entering the fifth intercostal space on the left and the fourth interspace on the right and transecting the sternum. Inset (*b*), purse-string sutures and tourniquets are applied to the right interatrial groove and the left ventricular apex. This right-sided approach is particularly useful in some cases of recurrent mitral stenosis or in instances in which palpation through the left atrial appendage is undesirable.

DISCUSSION

At present, transventricular dilatation of the mitral valve is performed in the majority of patients undergoing operation for mitral stenosis. The technique as described is safe and effective and insures adequate relief of the obstructive element in the valve. In only one case has mitral incompetence been produced by this technique, and in this patient the valve was dilated excessively.

The valve orifice in this case was extremely small and completely impenetrable by the usual finger fracture or digital dissection. The valvotome was used and the valve was suddenly opened to 5.0 cm., resulting in an anterolateral tear in the annular attachment of the leaflet. The valve was subsequently repaired using the pump-oxygenator for temporary cardiopulmonary bypass. In such instances, it is now recommended that the valve be dilated by degrees, beginning at 3.0 cm. and increasing the size cautiously as the valve is being palpated for evidence of incompetence. In none of our other cases, numbering approximately 18, has mitral incompetence been significant after operation. Indeed, in some patients with mild-to-moderate mitral incompetence demonstrable before operation, the signs of incompetence disappeared following the procedure. In instances in which chordae tendineae are stretched across the mitral orifice at the completion of finger dissection, use of the transventricular dilator is not advisable. Disruption of the chordae may result in mitral regurgitation.

Surgical attack upon recurrent mitral stenosis following previous mitral valvotomy, using various closed techniques, was generally unsatisfactory in our cases since the commissure in most of these cases was virtually impenetrable. Accordingly, 10 patients were operated upon using the pump-oxygenator for temporary cardiopulmonary bypass with one death[5] (Table I). In these cases the valve was approached from the right side of the heart, opening the left atrium widely. In most of the early cases, the valve was visualized and scissors were used to commence the commissurotomy. In each instance the valvotomy was completed using a large hemostat as a dilator. As experience accumulated, only the dilator was used with equally good results and without producing mitral regurgitation, even in the presence of severe calcification. An advantage of the open technique was that thrombi located in the left atrium could be carefully removed and, in one case, a fibrin coat of the atrium and a floating thrombus were removed. Extensive débridement of calcified deposits from the valve was not feasible. The principal disadvantage was the complication of air embolism which occurred in 3 patients in whom consciousness was regained 2

TABLE I. OPERATIVE RESULTS IN 10 PATIENTS UNDERGOING MITRAL VALVOTOMY DURING TEMPORARY CARDIOPULMONARY BYPASS

CASE	AGE	OPERATIVE FINDINGS	DATE OF PREVIOUS OPERATION	RESULTS
1. B. R.	22	Calcification	1953, 1955	Fair; moderate M. I.
2. L. K.	39	—	1954	Good
3. R. S.	45	Calcification, atrial thrombus	1952	Good
4. I. S.	36	—	1954	Good
5. O. W.	41	Ball valve thrombus	1951	Good
6. M. O.	38	—	1952	Good
7. M. D.	25	—	1954	Air embolism; died 7 days postop., pulmonary embolus
8. G. T.	39	Atrial thrombus	Exploratory thoracotomy 1958	Good
9. P. B.	29	—	Feb. 1958 Aug. 1958	Air embolism; good
10. S. J.	33	—	1956	Air embolism; good

days, 3 days, and 5 days, respectively, after operation (Table I). During the period of cerebral involvement there were generalized convulsive seizures, often associated with pulmonary edema. Although recovery of consciousness occurred in each of these cases, the complication was obviously a serious hazard in this approach. Because of this experience, in addition to the complexity of open heart surgery as opposed to closed techniques, cardiopulmonary bypass has been discontinued as a means of operating upon recurrent mitral stenosis. At present, all patients with recurrent mitral stenosis are operated upon by the bimanual transventricular technique.

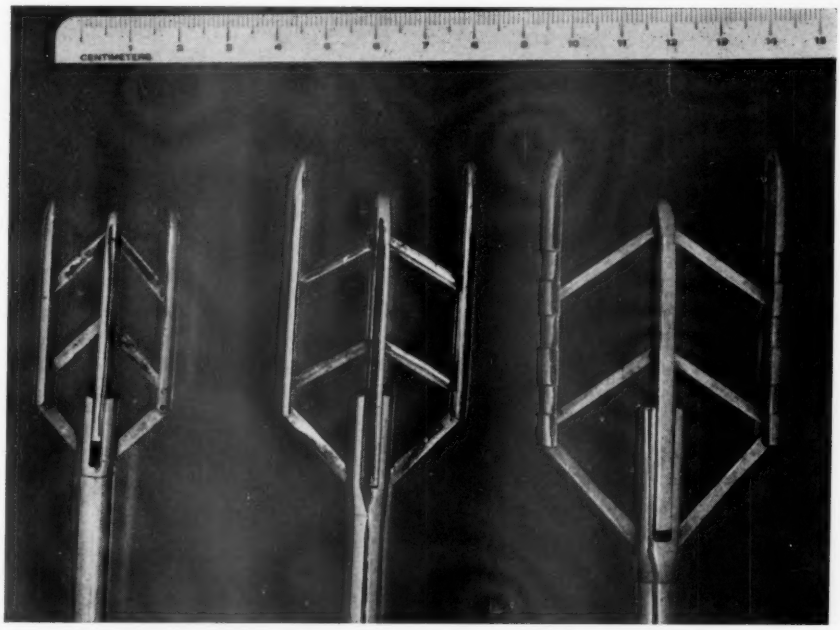

Fig. 3.—Photograph showing a set of expanding two-bladed dilators used in transventricular mitral valvotomy. Dilators have a maximum width of 3, 4, and 5 cm. In most instances, the 4 cm. dilator produces an adequate orifice and produces no mitral incompetence.

Dilatation of the mitral valve using an expanding dilator, introduced through the left atrial appendage, has been advocated by Dubost.[6] Introduction of the Dubost dilator is made after preliminary digital palpation and dilatation of the valve; thus, manipulation of the dilator inside of the heart and introduction into the mitral orifice are done blindly. Disadvantages of this method are apparent, such as faulty insertion into the valve and dislodgment of atrial thrombi—complications which could be avoided by the bimanual transventricular method.

The valvotomes used in our operations are of different sizes, ranging in width from 3.0 to 5.5 cm. (Fig. 3). The extent to which the valvotome is opened is determined by the size of the annulus and the degree of mitral valve insufficiency. The leading edge of the blades is beveled so that the instrument may be easily introduced through the ventriculotomy. Sufficient force may be exerted with the instrument to open even a densely calcified valve.

SUMMARY

A technique of mitral valvotomy is described in which an expanding dilator is inserted through the apex of the left ventricle. Palpation of the valvotome by the right index finger inserted into the left atrium insures accurate positioning of the instrument in the mitral valve. Transventricular valvotomy for recurrent mitral stenosis is preferred to open techniques in which the pump-oxygenator is used. Aortic and mitral valvotomy may be performed simultaneously through the ventricle using similar instruments.

ADDENDUM

Similar transventricular mitral valvotomy is employed by Logan of Edinburgh, Tubbs of London, Gerbode of San Francisco, and others.

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A NEW CLAMP FOR GASTROINTESTINAL SURGERY

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THE MANY types of clamps available for use in performing gastrointestinal surgery attest to the fact that there is no one satisfactory instrument. A common fault of most of them is that the stomach and small or large bowel have a tendency to slip out of the clamp when traction is applied. This may lead to spillage of gastric or intestinal contents into the wound. Slipping may cause the lumen of the partially clamped viscus to become distorted and may lead to a difficult and poor anastomosis.

Because of the deficiencies in existing gastrointestinal clamps, a new type of clamp was devised that eliminates the problem of slipping.

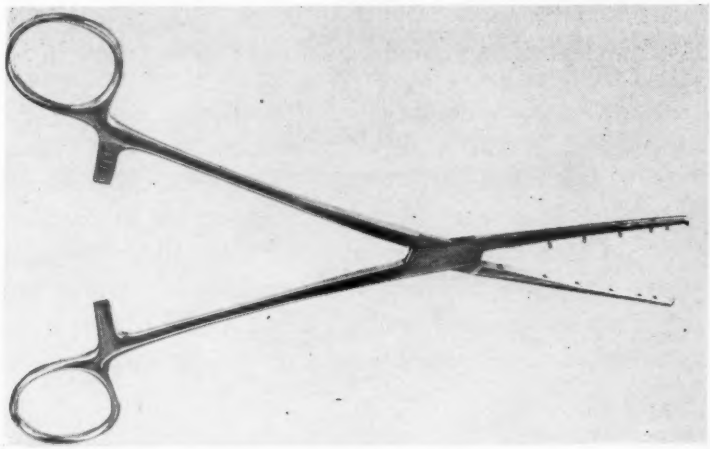

Fig. 1.—Photograph of gastrointestinal clamp. Detailed description is in text.

DESCRIPTION

The clamp resembles an Allen clamp in design. Its opposing jaws have longitudinal serrations and at its most distal extremity there is a sharp triangular tooth that fits into a receiving socket on the opposite blade. Along the surface of the inferior blade there are 5 holes, 1 mm. in diameter. The first of these is 5 mm. from the distal tooth; the second is 5 mm. meters from the first; the others are 9 mm. apart from each other. On the superior blade, there are 5 rounded peg-like protrusions slightly less than 1 mm. in diameter and 2 mm. in length. These are spaced to be directly opposite the holes on the inferior blade and fit into these holes when the jaws of the clamp are closed.

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The segment of stomach or bowel is held securely in the clamp by the bite of the 5 pegs (Fig. 1).* An instrument for gastrectomy with a similar jaw design was described by McElmoyle[1] but has not come into popular use.

DISCUSSION

The clamp should be applied in such a way that the blade containing the holes is placed beneath the viscus and the pegged blade on top. This provides easy application of the clamp. The clamp cannot be pulled away from the divided stomach or bowel after it has been applied. The portion of the viscus in the jaws of the clamp is inverted and will slough, as with the use of any of the other clamps now available. Release of the clamp is no more difficult than with any of the gastrointestinal clamps currently utilized. The clamp described has been used extensively in the research laboratory and in many gastric and large and small intestinal anastomoses in operations on human beings. It has been found to eliminate slipping of stomach or bowel at the time that anastomosis is performed.

SUMMARY

1. A clamp is described for use in performing anastomosis in gastrointestinal surgery that is designed not to slip.

2. The instrument has been found to be very satisfactory in both laboratory and clinical trials.

REFERENCE

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*The clamp is available in various sizes from Codman and Shurtleff, Inc., 104 Brookline Ave., Boston 15, Mass.

Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

DECOMPENSATED SMALL BOWEL: TUBE JEJUNOSTOMY IN THE SURGICAL TREATMENT OF JEJUNAL ATRESIA

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THE NUMBER of babies in the United States with bowel atresia, who succumb after operation or who succumb without operation, is estimated by Wilson and his associates[14] to be 2,200 annually. Few surgeons are privileged to acquire an extensive personal experience. It is apparent, however, with even a limited experience, that one of the problems encountered is the persistence of obstructive symptoms in spite of an apparently adequate operation. Mortality (as high as 66 per cent) is frequently attributed to local complications, either disruption at suture lines or "functional" obstruction.[13] The condition of these children is often so desperate that the opportunity is seldom given to reoperate in apparent failures. At the autopsy table, the finding of an apparently patent anastomotic stoma which has not functioned has been seen and is indeed said by Wilson,[14] and by Gerrish and co-workers[4] to be a common cause of failure. Death occurring 5 to 8 weeks after definitive anastomosis with a patent anastomosis but a persistently dilated proximal bowel is known to students of the problem.[13]

Few of these cases are reported in detail.[4] It is felt that because of the sequence of events which occurred in this patient, and the opportunity which presented itself to observe the behavior of two anastomoses performed in the same patient in somewhat different fashion, a detailed report should be made.

CASE REPORT

B. A. F. was a 48-hour-old full-term female infant who developed abdominal distention and vomiting of bile-stained fluid. The roentgenogram (Fig. 1) revealed only a gas-distended stomach, duodenum, and upper jejunum, which suggested jejunal obstruction. Operation revealed jejunal atresia at about the junction of the upper and mid third. The dilated bowel was decompressed through a jejunotomy. The junction of the dilated and collapsed bowel was transected. Patency of the collapsed bowel was demonstrated by injection of saline solution intraluminally. Side-to-side anastomosis between dilated and collapsed bowel was performed in isoperistaltic fashion with interrupted sutures of 5-0 silk,

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over a No. 16 Fr. catheter, in two layers (Fig. 2, *A*). Patency of the stoma was demonstrated and the abdomen closed in layers. Nasogastric suction and intravenous fluids were continued postoperatively. By the fifth postoperative day, it was apparent that the obstruction was unrelieved (Fig. 3) perhaps because the bowel beyond the anastomosis had kinked.[6] A second laparotomy revealed a T-shaped kink in the collapsed small bowel just distal to the site of anastomosis, which was considered to have been responsible for recurrence of obstruction (Fig. 2, *B*). Because of the child's desperate condition it was decided to perform the shortest possible procedure to relieve obstruction and combine it with a tube jejunostomy, for possible jejunostomy feedings into the collapsed small bowel. Side-to-side anastomosis in isoperistaltic fashion between a loop of collapsed jejunum and the uppermost dilated jejunum (Fig. 4, *A*) was done. A polyethylene catheter of 2 mm. internal diameter was threaded from dilated jejunum, through the site of anastomosis, into collapsed jejunum just before completion of the innermost layer of the anastomosis. The catheter was brought out through a small opening in the abdominal wall. The site of the tube jejunostomy was sutured to the parietal peritoneum. The wound was closed with through-and-through cotton sutures. By the third postoperative day, the child now being 10 days of age, a small amount of gas was noted in the collapsed jejunum on roentgenogram, and oral feedings were started. Since there had been marked distention and thickening of the bowel proximal to the most recent anastomosis, in spite of continuous nasogastric suction, the jejunostomy tube was pulled back into the dilated jejunum just above the anastomotic site to decompress this loop following feedings (Figs. 4, *B*, and 5). The nasogastric tube was removed. Oral feedings followed intermittently by decompression of the upper jejunum through the enterostomy tube was continued for a period of 14 days. Returns consisted mainly of gas under pressure and small volumes (2 to 20 c.c.) of small bowel contents. On removal of the enterostomy tube, the fistula closed spontaneously. Oral feedings were gradually increased. Nine days after the second operation, Lipiodol instillation through the jejunostomy catheter revealed an apparently well-functioning anastomosis, the upper jejunojejunostomy. The child was now eating ravenously and the bowels were moving. There was no abdominal distention. She was discharged from the hospital 23 days after her second operation and was readmitted one week later because of a cold. In rapid succession, during the next 2 months, she developed a *Staphylococcus aureus* abscess of the buttock, bronchiolitis, and a *Staphylococcus aureus* septicemia. Diarrhea and recurrent abdominal distention finally supervened. The distention was most marked following feedings and interfered with respiration and nutrition. Radiographic study of the gastrointestinal tract (Fig. 6) revealed that the upper anastomosis functioned well but a greatly dilated loop of jejunum, presumably the segment bypassed at the child's second operation, probably accounted for the abdominal distention. At age 3 months, a third operation revealed (Fig. 7, *A*) that the upper jejunojejunostomy had functioned well while the loop of jejunum proximal to the original anastomosis was distended and contained a large volume of partially digested milk. The previous site of kink had straightened completely. On removal of the specimen it was apparent that the anastomosis was widely patent, permitting the introduction of a probe 4 mm. in diameter, while there was no evidence of intestinal contents ever having passed through it. The greatly dilated and collapsed jejunal loops were resected. Fig. 7, *B* shows the final reconstruction of the bowel.

The child made an uneventful recovery and has been well since, at age 2½ years.

DISCUSSION

The striking difference in the behavior of the two anastomoses performed in this child, with the final demonstration of the fact that the nonfunctioning anastomosis was nevertheless mechanically patent, emphasizes a concept which has most recently been described by Gerrish.[4] He states that one of the requisites for performing successful anastomoses in children with atretic bowel is that

Fig. 1.—Preoperative roentgenogram of abdomen showing gas pattern of high small bowel obstruction. Diagnosis of jejunal atresia made at age 2 days. Laparotomy performed.

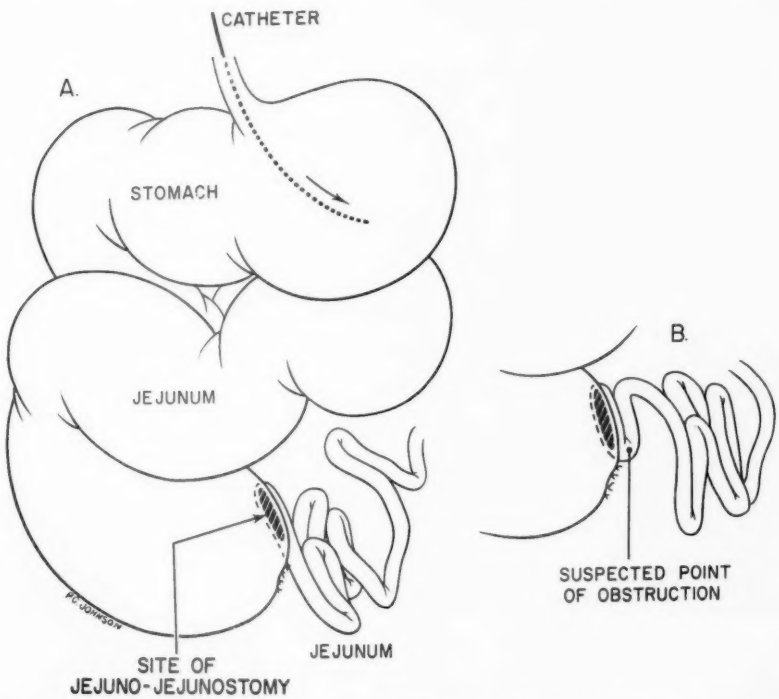

Fig. 2.—*A*, Diagrammatic representation of first jejunojejunostomy performed in side-to-side fashion for jejunal atresia (age 2 days). *B*, Mechanism of recurrent obstruction found at second laparotomy (age 7 days).

Fig. 3.—Radiologic appearance of recurrent small bowel obstruction just prior to second laparotomy (age 7 days).

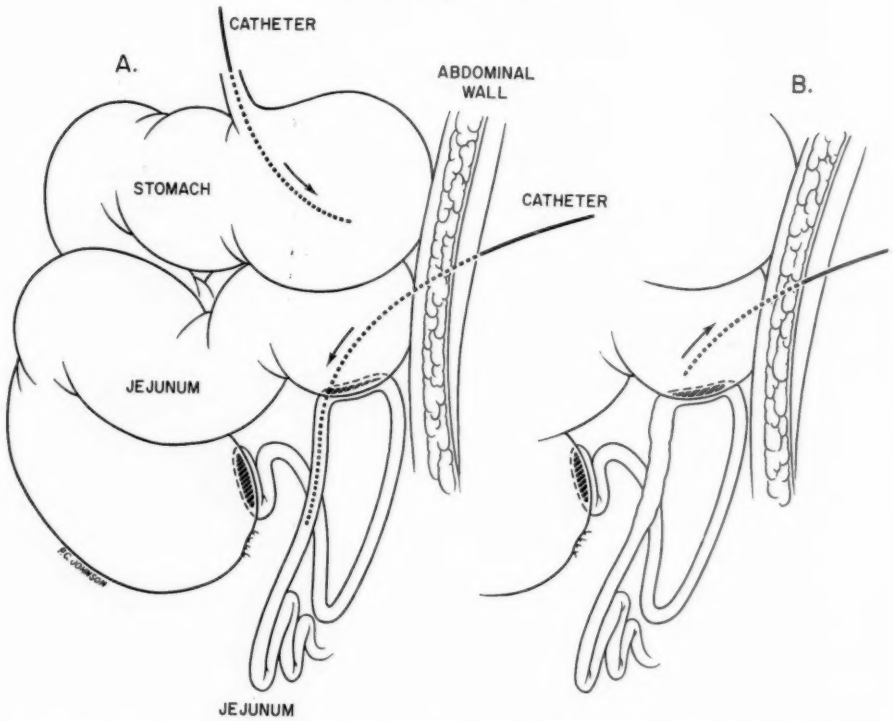

Fig. 4.—*A*, Diagrammatic representation of side-to-side high jejunojejunostomy performed at second laparotomy. Tube jejunostomy with tube placed through anastomosis into collapsed jejunum (age 7 days). *B*, Withdrawal of catheter into dilated jejunum just proximal to the anastomosis for decompression of greatly dilated jejunum (age 10 days). Decompression continued for 12 days.

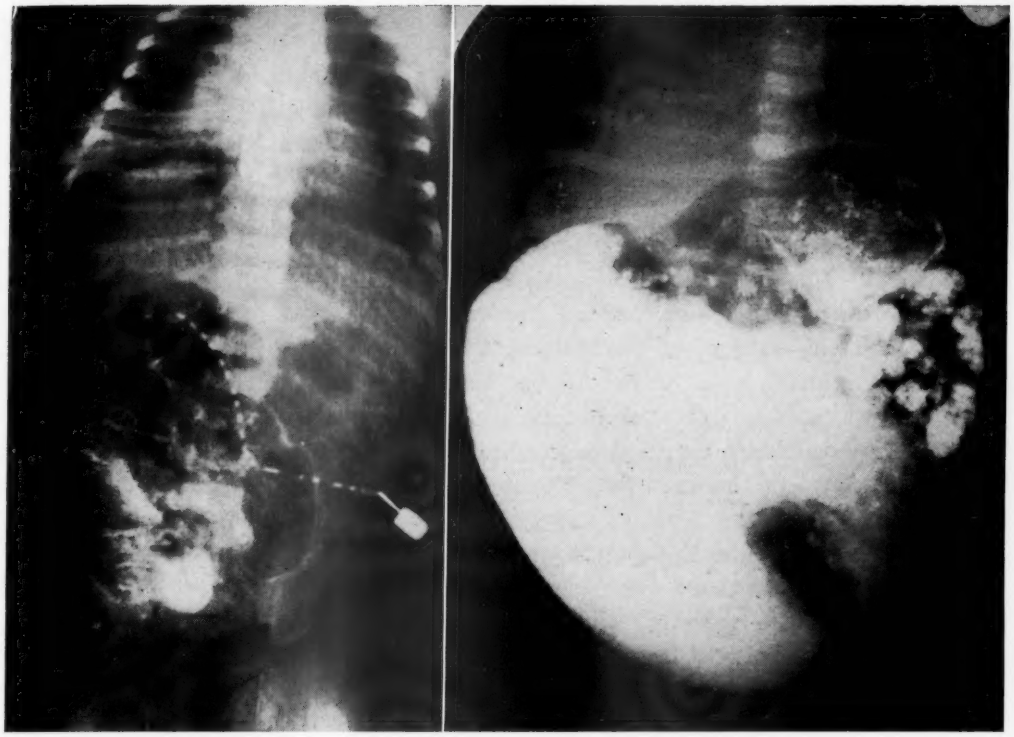

Fig. 5. Fig. 6.

Fig. 5.—Roentgenogram which shows position of catheter in dilated loop of jejunum.

Fig. 6.—Roentgenogram of abdomen with contrast medium to show greatly dilated jejunal loop (age 2 months).

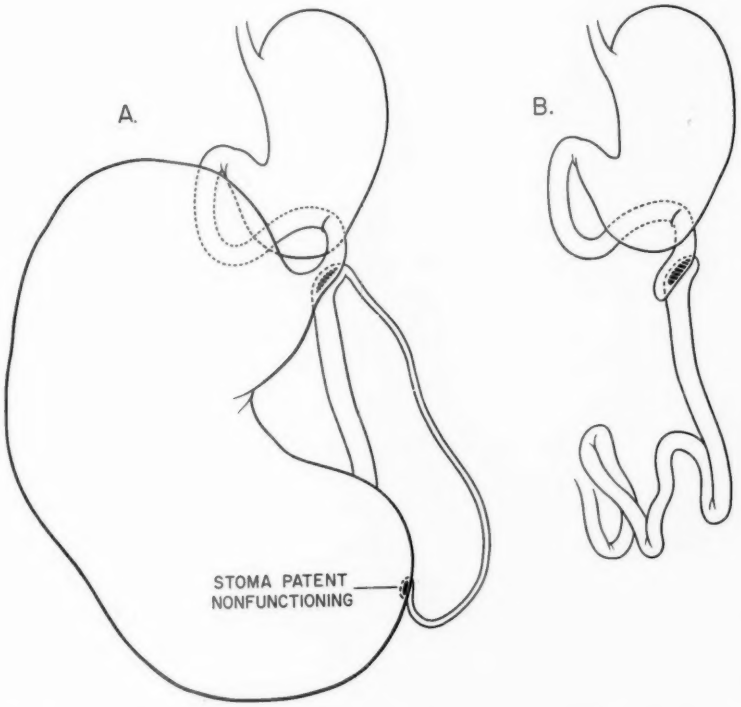

Fig. 7.—*A*, Diagrammatic representation of findings at third operation with greatly dilated jejunal loop in spite of mechanically patent stoma (age 9 weeks). *B*, Final reconstruction of gastrointestinal tract. Child remains well at age 2 years.

adequate decompression of the greatly dilated proximal loop must be maintained so that it can attain its ability to contract effectively. Other authors have suspected that this was of importance and that failure to do so helped to explain the frequently made observation that some children with apparently adequate surgical procedures will die of postoperative "ileus," namely, unrelieved obstruction, and at autopsy will have mechanically patent anastomoses.[4, 13, 14] In others, death from peritonitis occurs from disruption at suture lines apparently because of marked distention of the proximal loop. It is our opinion that the success of the second anastomosis in this child was entirely due to the maintenance of decompression just proximal to the anastomosis. It is our feeling, too, that the higher incidence of success attendant upon the treatment of duodenal or duodenojejunal junction obstructions is attributable, at least in part, to the fact that the nasogastric tube, now almost universally used in these infants postoperatively, is effective in decompressing the duodenum, at least below the degree of distention beyond which decompensation occurs and restoration of effective peristalsis will not occur. Else why the introduction of the various "long" intestinal tubes for small bowel obstructions? As early as 1933, R. F. Carter[3] used enterostomy tubes for decompression of the proximal dilated loop in children with bowel atresia. Since then other authors[4, 5, 9] have advised a similar adjunct to primary anastomosis. Others[7, 8, 12] have suggested the possibility of using this type of decompression via Miller-Abbott tubes.

There is evidence to suggest[2] that acetylcholine is produced by the intestinal wall, independent of nervous activity, and that it may have physiologic effects also independent of nervous activity. The accumulation of acetylcholine, apparently to some threshold level, is followed by muscle contraction. Feldberg[2] postulates that the acetylcholine produced by the cells of the various layers of the bowel wall not only stimulate muscle cells and gland cells within the bowel wall but possibly nerve cells as well to keep them in a continuous state of tonic activity.

If this be so then, one might postulate, to help explain the apparent nonfunction of the mechanically patent original jejunojejunostomy, that distention of the bowel beyond a particular stage resulted in a failure of the bowel wall to produce acetylcholine. Spontaneous recovery did not occur because a certain stage of decompensation had been reached which we feel could have been reversed by keeping that portion of the bowel decompressed.

There have been a number of recent reports[1, 11, 12] of the successful management of lower small bowel atresias which have involved the resection of the most distal portion of the dilated loop prior to the performance of the usual enteroenterostomy. It is conceivable that what is being accomplished is that the most dilated portion of the bowel, dilated to the stage of decompensation, is being removed and anastomosis is performed to bowel which has not yet become decompensated.

Insofar as the treatment of these children is concerned, many of whom are premature, many deathly ill, the immediate achievement and maintenance of

adequate bowel decompression seems to be of paramount importance for survival. Tube enterostomy in this particular case appears to have achieved this.

It is hoped that some of the questions raised by the observations made in this case may be answered experimentally. Is there a stage of decompensation? How long is the lag period between decompensation, decompression, and recovery? How much of the dilated bowel participates in the reaction? What are the means by which it can be overcome?

SUMMARY

A case is presented of multiple operations for jejunal atresia with eventual recovery. The successful outcome is attributed to the performance of a tube jejunostomy to decompress a second jejunojejunostomy after the first such procedure had failed. The operative findings are illustrated in detail.

Acknowledgment is made to Dr. George Rostel, now of Santa Rosa, Calif., who referred the patient for treatment and provided the extensive and lengthy pediatric care without which this child could not have survived.

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JEJUNOILEAL ATRESIA AND STENOSIS

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JEJUNOILEAL ATRESIA and stenosis form an interesting and important group of congenital malformations in that the gastrointestinal tract is usually the only organ involved and, if the defect is corrected, a normal life span should be expected. However, the mortality rate reported in two large series from this country has been high (Gross[5] reports 35 surviving infants out of 66, 1940 to 1952; Santulli,[9] 7 surviving infants out of 25, 1939 to 1952). More recently a number of authors[1, 4, 7] have recorded an increased survival rate in a smaller number of cases, and, without question, more refined methods of pre- and postoperative care, anesthesia, antibiotics, and operative technique have contributed much to their success. Still, there are certain features regarding the management of these infants that deserve emphasis.

The purpose, therefore, of this report is to record briefly our experience with a group of these infants at the University Hospitals, Madison, Wisconsin, and to present in detail certain factors that we consider important in reducing the high mortality usually associated with the surgical management of these cases.

MATERIAL

The clinical records of 10 infants, in whom the diagnosis of jejunoileal atresia or stenosis was confirmed at operation, were reviewed. The pertinent data concerning these infants are summarized in Table I.

Seven were males and 3 were females; 6 infants weighed less than 6 pounds at birth, and 3 were considered by pediatric standards to be premature. Atresia of a given segment of jejunum or ileum accounted for 8 cases; stenosis of the ileum for 2. The most common segment of the bowel to be involved was the jejunum. In two instances, the atresia or stenosis was complicated by other gastrointestinal abnormalities; in 1 case Meckel's diverticulum with perforation and localized muconium peritonitis was observed, and, in the other, multiple atretic segments of jejunum in association with malrotation of colon.

CLINICAL FINDINGS

The most frequent and significant symptom manifested by the infants in our series was bile-stained vomiting, and all 10 infants presented this condition within 24 hours after birth. In most instances, the importance of this symptom was not appreciated, and, as a supplementary observation, the initial

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TABLE I

NAME	SEX	WEIGHT AT BIRTH	DELAY IN DIAGNOSIS	LOCATION OF ATRESIA OR STENOSIS	PROCEDURE	RESULTS
F. M.	M	10 lb.	4 days	Atresia, proximal ileum	Side-to-side anastomosis	Lived
R. F.	M	6 lb. 12 oz.	3 days	Atresia, mid-jejunum	End-to-end anastomosis	Lived
M. P.	M	4 lb. 15 oz.	1 day	Atresia, proximal ileum	End-to-end anastomosis	Lived
J. D.	F	5 lb. 13 oz.	2 days	Atresia, mid-ileum	End-to-end anastomosis	Lived
R. N.	M	5 lb. 15 oz.	5 days	Atresia, mid-ileum	End-to-side anastomosis	Lived
J. W.	M	8 lb. 1 oz.	6 days	Stenosis, mid-ileum	Side-to-side anastomosis	Lived
C.C.	M	5 lb. 4 oz.	2 days	1. Atresia, proximal ileum 2. Meckel's diverticulum 3. Localized area of muconium peritonitis	Side-to-side anastomosis	Expired 10th day
R. C.	F	4 lb. 11 oz.	3 days	1. Atresia, upper jejunum 2. Three areas of atresia 3. Malrotation of colon	Side-to-side anastomosis	Expired 2nd day
P. L.	M	5 lb. 5 oz.	3 days	Atresia, distal jejunum	End-to-end anastomosis	Expired 2nd month
J. P.	F	5 lb. 13 oz.	20 days	Stenosis, mid-ileum	Ileostomy	Expired 1st day

feeding of these infants almost invariably increased the vomiting. Furthermore, projectile vomiting was seldom noted, and frequently the terms "drooling" or "spitting up" of bile-stained material were used by parents and nurses to describe the infant's condition.

Additional symptoms during the first 24 hours of life were rather meager, and the infants were considered otherwise normal. During the thirty-sixth to seventy-second hour of life, abdominal distention, visible peristaltic waves, absence of normal stools, and signs of dehydration became evident and increased with time.

Laboratory and clinical examination of the blood appeared to be of little help in the diagnosis, and, in most instances, the electrolyte disturbance was quite similar to that observed in adults with intestinal obstruction.

A plain roentgenogram of the abdomen was the most reliable diagnostic procedure, and in all of our cases this demonstrated evidence of small bowel obstruction, manifested principally by dilated loops of gas-filled small bowel, fluid levels, and absence of gas pattern in the colon. The employment of contrast material on three occasions did not appear to facilitate the diagnosis.

In 9 instances, bowel continuity was established by a primary anastomosis; in 1 patient an enterostomy was the only operative measure employed. Six of the 10 infants in our series survived. Of the 4 infants who died a postmortem record was obtained in 3 instances. From the clinical and postmortem data,

a number of factors, both direct and indirect, were found responsible for the death of these infants; the most common were (1) delay in diagnosis, (2) prematurity, (3) pneumonitis, (4) electrolyte and nutritional imbalance, (5) hepatic necrosis, (6) circulatory failure, and (7) a leak or failure of the anastomosis to function.

DISCUSSION

The composition of our series and the factors responsible for the high mortality rate agree on the whole with that reported from other quarters,[5, 6, 7, 9] namely, leaks or failure of the anastomoses to function, delayed diagnosis, prematurity, pulmonary complications, and nutritional and electrolyte imbalances.

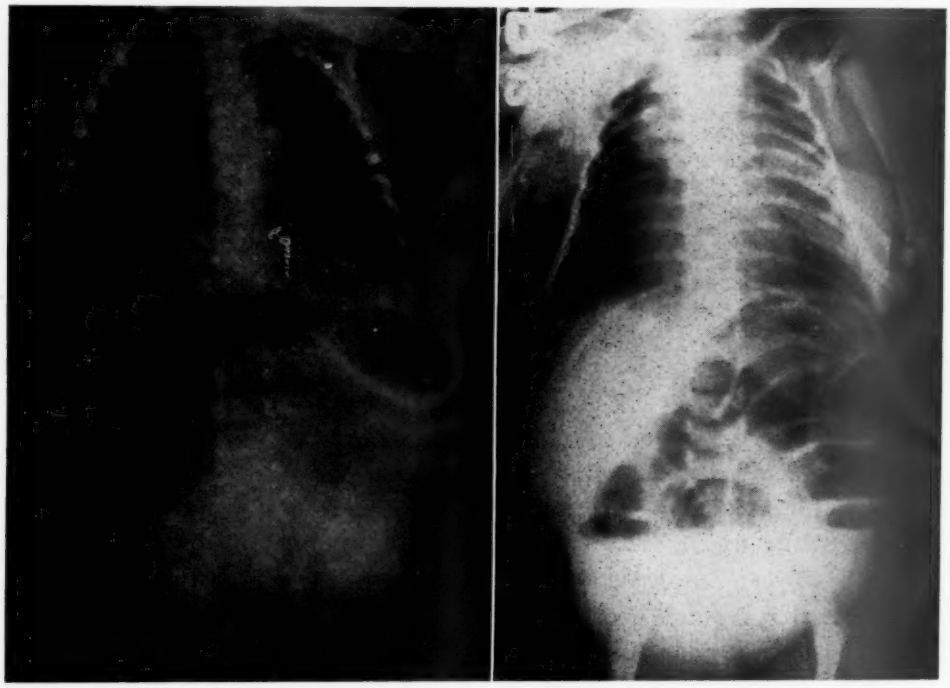

Fig. 1. Fig. 2.

Fig. 1.—A film of an infant, in an upright position, with jejunal atresia which shows the extensive small bowel distention and absent colonic gas pattern that accompanies this condition.

Fig. 2.—A plain film of the abdomen showing many loops of small bowel indicating an obstruction in the ileal segment.

The exact role of each of these factors in contributing to the cause of death was difficult to evaluate, for, in most instances, combination of two or more of these factors has been noted in the clinical and postmortem records. However, a review of cases here and elsewhere has indicated that delay in diagnosis and leak of the anastomosis or its failure to function have been the two causes most directly responsible for the death of these infants.

Delay in diagnosis and its untoward effect on newborn infants with conditions of this nature are well known. In our series, and in other collected series of this kind,[1, 6, 9] a delay of 3 days or more has been a frequent finding. Nevertheless, the clinical features of jejunal and ileal atresia and stenosis

have been quite characteristic in that green bile-stained vomitus was observed during the first 24 hours of life. Nixon,[7] Gross,[5] Potts,[8] and others have emphasized the importance of this single diagnostic feature and have pointed out that vomiting of bile-stained gastrointestinal contents seldom occurs in healthy newborn infants.

Furthermore, Nixon,[7] in a survey of 106 newborn infants, found 23 who vomited during the first 7 days of life, and in 8 instances the vomitus was yellow and not green; chemical tests for bile were negative in each instance. His statement, "A green, bile-stained vomit should be considered an indication for investigation and not further observation," is worthy of repetition.

It is our own feeling that in the majority of instances these infants appear quite healthy and thus lead the physician to a false sense of security with respect to the underlying small bowel obstruction. Still, the fact remains that bile-stained vomitus is pathologic and requires further investigation. In this regard, a plain roentgenogram of the abdomen appears to be the most useful diagnostic measure to employ, and in our series evidence of a small bowel obstruction was unequivocal in each instance in which it was employed.

The second, and probably the most important, factor responsible for the mortality rate in these infants has been leak or failure of the anastomosis to function. Early writers attributed this condition to the failure of the distal, contracted bowel to function in a normal manner once bowel continuity was established. More recently, however, a number of investigators[1, 4, 6, 7] have suggested that the underlying mechanism is due to the inability of the dilated, hypertrophied proximal small bowel to propel the intestinal contents distalward.

Louw,[6] one of the first to recognize this condition, suggested that the dilated proximal bowel is atonic as a result of the prolonged duration of the obstruction. Nixon,[7] however, has shown that this portion of the bowel has peristalic activity and, in a series of laboratory experiments, demonstrated that bowel of this nature requires an intraluminal pressure, much in excess of normal, to initiate peristalsis. Gross,[5] however, tends to implicate the formation of adhesions about the anastomotic site as the obstructive factor.

Whichever explanation may be correct, we believe that decompression of the dilated, hypertrophied, proximal intestine is necessary if a functioning anastomosis and gastrointestinal tract are to be obtained. At present three methods of approach to the problem have been described: (1) exteriorization (Mikulicz procedure) without primary anastomosis,[5] (2) the use of infant Miller-Abbott tube[9] or insertion of an enterostomy tube in the proximal dilated bowel with primary anastomosis,[4, 12] and (3) excision of the dilated proximal bowel followed by primary anastomosis.[1, 7] By each method, direct or indirect decompression of the proximal loop is effected.

To judge by the available surgical literature, no one method has become established as the ideal procedure. In Table II is listed a series of reported cases treated by one of the three procedures mentioned; the results with respect to survival rate are quite identical. Gross,[5] however, has shown in an analysis of his cases, that a Mickulicz exteriorization procedure is the superior method

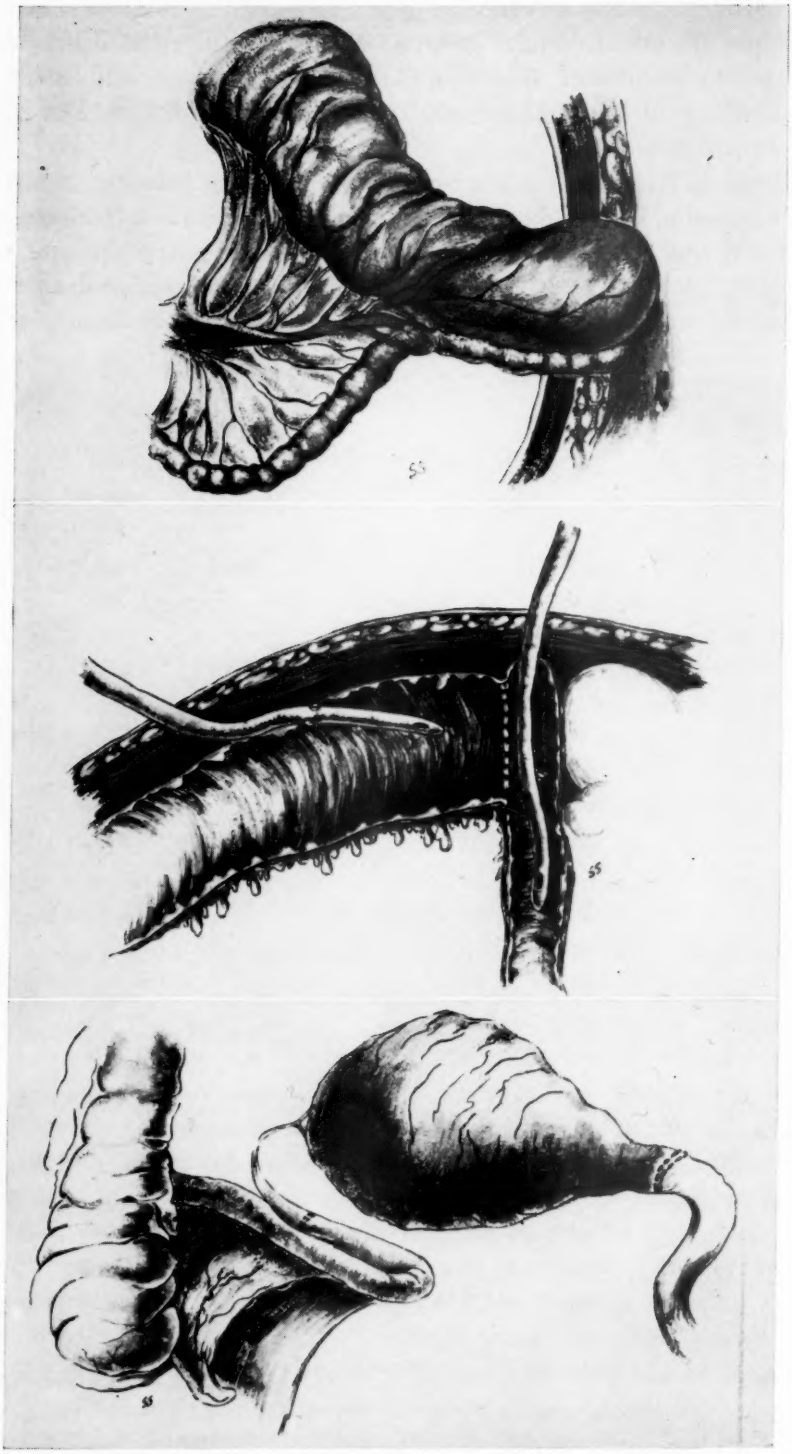

Fig. 3.—Methods commonly employed in the surgical management of jejunoileal atresia and stenosis. *A*, Exteriorization (Mikulicz procedure). Each limb of the double-barrelled enterostomy is opened after the abdominal wound is closed. *B*, Decompression of the proximal dilated bowel with an enterostomy tube, following anastomosis of the dilated proximal bowel to the distal contracted segment. A feeding tube has been placed in the distal bowel for the purpose of replacing fluid lost from the enterostomy. *C*, The large, dilated, edematous proximal bowel segment is resected to grossly normal-appearing bowel (as indicated by the dashed lines), anastomosed end-to-end.

of management for ileal atresia. Still others[1, 3, 4, 7, 10, 11] have approached his survival rate, in a much smaller number of cases, by employing either an enterostomy tube decompression of the proximal dilated bowel or excision of same, with primary bowel anastomosis in each instance. The authors who have advocated these latter methods point out that an exteriorization Mickulicz procedure prolongs the period of hospitalization, requires a second operation, and, most important, increases the difficulty in managing the fluid and electrolyte losses that are associated with an enterostomy in infants of this age. In our experience, an exteriorization of a loop of bowel for conditions other than atresia and stenosis has not been entirely satisfactory because of this latter problem.

TABLE II. A COMPARISON OF VARIOUS TECHNIQUES EMPLOYED IN THE TREATMENT OF JEJUNOILEAL ATRESIA AND STENOSIS, SHOWING THE NUMBER OF SURVIVING INFANTS AS REPORTED BY VARIOUS AUTHORS

RESECTION OF DILATED PROXIMAL BOWEL FOLLOWED BY A PRIMARY ANASTOMOSIS			ENTEROSTOMY TUBE DECOMPRESSION OF PROXIMAL BOWEL OR EXTERIORIZATION (MIKULICZ PROCEDURE) WITH OR WITHOUT PRIMARY ANASTOMOSIS		
AUTHOR	TOTAL NUMBER OF CASES	NUMBER OF INFANTS SURVIVED	AUTHOR	TOTAL NUMBER OF CASES	NUMBER OF INFANTS SURVIVED
Nixon[7]	15	10	Gross[5] (Ileal atresias)	20	14
Swenson[10]	4	4	Tuschka[12]	3	2
Benson[1]	14	10	Duckett[3]	5	5
Synder[11]	5	5	Gerrish[4]	10	7
Total	38	29		38	28

It is to be noted when decompression of the proximal loop is established, whether by proximal enterostomy tube, exteriorization Mikulicz procedure, or excision of the dilated proximal bowel with primary anastomosis, the survival rates are comparable.

Because of the small number of cases in our series, we are unable to make any conclusion as to a procedure of preference. We feel that excision of the proximal dilated bowel with end-to-end anastomosis, or an enterostomy tube decompression of the proximal bowel with primary anastomosis (we prefer the former), are both physiologically sound procedures when employed in the light of our present-day knowledge concerning the pathophysiology of jejunoileal atresia and stenosis, and wound healing in general.

The many other additional measures required to maintain these infants during the preoperative, operative, and postoperative periods have been reviewed by many authors.[5, 7, 9] It is our opinion that the two factors most directly responsible for the high mortality associated with the management of jejunoileal atresia or stenosis in the newborn are (1) the adverse cumulative effects resulting from the delay in diagnosis, and (2) the failure to recognize the altered intestinal physiology of the bowel when establishing bowel continuity by surgical methods.

SUMMARY

A series of 10 cases of jejunoileal atresia and stenosis in the newborn infant is analyzed.

The significance of bile-stained vomitus and the use of plain x-ray of the abdomen in the diagnosis of this condition is emphasized.

The methods of surgically managing these infants are discussed, and it is suggested that treatment be directed to the employment of techniques that will insure adequate decompression of the proximal dilated small bowel. Whether this is best accomplished by a Mikulicz type of exteriorization procedure, an enterostomy decompression tube of the proximal bowel, or complete excision of the dilated proximal loop with primary anastomosis has yet to be established. At present, we prefer the latter method of treatment.

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ISOLATED MIDLINE THYROID IN THE THYROGLOSSAL DUCT

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ISOLATED midline thyroid nodules may be confused with thyroglossal duct cysts and excised with resulting myxedema. An awareness of the possibility of this congenital anomaly may prevent such an error. The following case report is offered as an example of this condition and as a reminder of the potential hazard involved in the removal of a midline nodule in the neck.

CASE REPORT

A healthy 6-year-old Negro girl was admitted on the Halsted Surgical Service for the removal of a midline cervical nodule present since birth. This mass had retained its relative size with the child's growth, had never been infected, and had never drained. Because of the cosmetic deformity she was admitted for elective excision. A round, rubbery, smooth, midline mass one inch in diameter was noted immediately below the hyoid bone to which it was loosely adherent (Fig. 1, *A* and *B*). It was nontender. It was not attached to the overlying skin or subcutaneous tissue and moved slightly upward when the tongue was extruded. There was no palpable mass at the base of the tongue. The patient was considered to have a typical uninfected thyroglossal duct cyst.

Under endotracheal ether anesthesia a 2-inch transverse incision was made overlying the mass which was exposed beneath the anterior cervical fascia. The mass was grayish red with several dilated veins emerging from each lateral surface. Because of its consistency and unusually rich blood supply, the nodule was thought to be the superior portion of the pyramidal lobe of the thyroid. The strap muscles were retracted to visualize the normal thyroid lobes, but no thyroid tissue was present in either lateral fossa. When it became apparent that the mass represented the total thyroid tissue, it was carefully elevated from the trachea and the bilateral superior thyroid vascular pedicles were identified and mobilized laterally (Fig. 1, *C*). The mass was then bisected in the midline, several bleeding points were suture ligated, and the two halves were inserted into the lateral thyroid fossae, which had been deepened by stretching the overlying strap muscles (Fig. 2). The wound was then closed with fine silk. Histologic examination of the biopsy taken from the mass showed normal thyroid tissue. The patient was discharged from the hospital the following day and continued an uneventful recovery. Six months following operation there was no evidence of hypothyroidism and a very satisfactory cosmetic result was noted (Fig. 1, *D* and *E*).

DISCUSSION

In the 105 cases of thyroglossal tract anomalies reviewed by Ward and associates,[6] only 6 contained fragments of thyroid tissue. One intralingual cyst apparently contained all of the patient's thyroid gland, for after removal the 14-year-old boy was myxedematous and continues to require thyroid extract 21 years after the cyst excision. Gross[2] reported a series of 198 cases of

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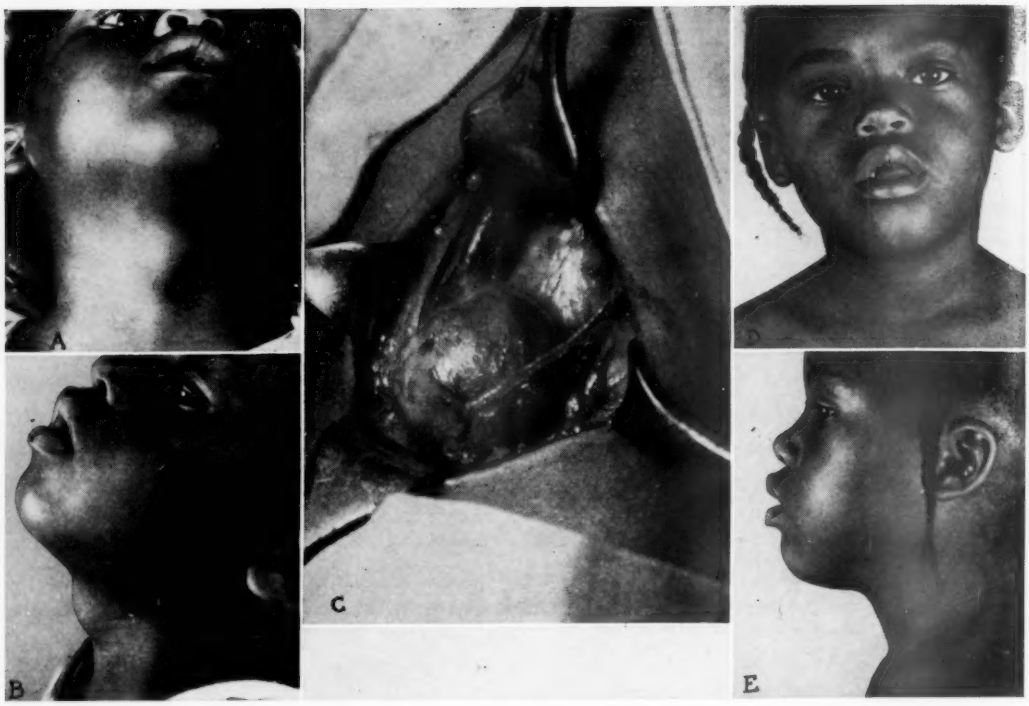

Fig. 1.—*A* and *B*, Preoperative photographs of patient with midline cervical nodule. *C*, Operative photograph of biopsy proved isolated midline thyroid. *D*, and *E*, Postoperative photographs of patient at 6 month follow-up visit.

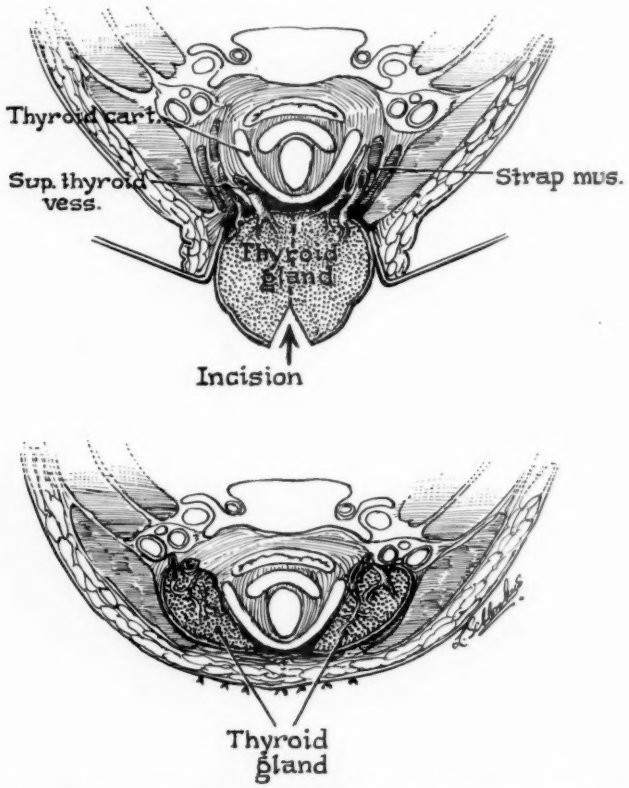

Fig. 2.—Diagrams of anatomic relationships and method of bisection of thyroid mass with bilateral implantation.

thyroglossal duct excision, in one of which the excised mass apparently represented the only thyroid tissue in the patient. This patient also became myxedematous following excision and still requires thyroid extract. Gross has had two more recent cases of midline thyroid nodules, which were fortunately recognized as such and handled in a manner similar to the case reported here.[1] In his further comments on these 3 cases Gross emphasized the necessity of aspirating or biopsying the atypical nodule and, if thyroid tissue is present, carefully exploring the lateral fossae before excision.

The embryology of the thyroid gland and its descent through the neck is well-known, but a failure of normal lateral lobe formation when the medial thyroid anlagen fail to descend is not constant and not well understood.[4] This failure of descent from the foramen cecum level, which may result in a lingual thyroid, does not exclude the presence of normal lateral lobes, but the high incidence of myxedema following removal of lingual thyroid tissue suggests that normal lateral thyroid tissue is rarely found. Thus patients with large lingual thyroid glands must be considered to have no thyroid present in the normal neck position.[3, 5] Many such cases of midline lingual thyroid have been reported and every attempt has been made to preserve this tissue unless its bulk produced obstruction in the hypopharynx or ulceration resulted in serious hemorrhage. Location of the thyroid gland in the position of a thyroglossal duct cyst in this child is similar to the cases of lingual thyroid in that there was no identifiable lateral gland and myxedema would have resulted had its true nature not been recognized and the tissue preserved.

CONCLUSION

Isolated midline thyroid tissue may occur anywhere between the base of the tongue and the suprasternal notch. It is usually confused with a thyroglossal duct cyst or benign tumor and is excised. The resulting myxedema is an emphatic but belated reminder of the necessity for careful identification of both thyroid lobes prior to removal of any such atypical cervical mass.

The problem has been illustrated by several cases from reported series of thyroglossal duct excisions in which myxedema developed following mistaken removal of the sole thyroid tissue in the position of a thyroglossal duct cyst. The proper handling of this problem is exemplified by this little patient in whom the midline thyroid tissue was split and each half with its vascular pedicle was inserted in a recess developed beneath the strap muscles.

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MECKEL'S DIVERTICULUM: THE ABDOMINAL MASQUERADER

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INTRODUCTION

OCCURRING in 1 out of 50 persons, Meckel's diverticulum usually remains hidden but may emerge wearing various disguises. This small appendage delights in causing the borborygmus clamor of an acute intestinal obstruction on one occasion, while at another time it may assume the pallid countenance of an unexplained anemia. Even when simulating the McBurney point pain of acute appendicitis, the masquerader succeeds in deceiving nearly everyone. A review of the experience at the Buffalo Children's Hospital for the past 15 years was undertaken to provide a glimpse behind this mask.

Sixty-one children underwent removal of a Meckel's diverticulum for various causes (Table I). Fifteen operations were performed for gastrointestinal tract bleeding and 17 for obstructive lesions. Twenty-two children were operated upon either for acute or chronic abdominal pain. One infant had excision of a Meckel's diverticulum because of a draining umbilical sinus and on 6 others, diverticulectomies were performed incidental to other operative procedures.

TABLE I

Anemia	15 cases
Intestinal obstruction	17 cases
Abdominal pain	
Perforation with peritonitis	7 cases
Recurrent pain	15 cases
Draining umbilical sinus	1 case
Incidental	6 cases
Total	61 cases

CLINICAL MATERIAL

In studying our cases of Meckel's diverticulum at this hospital, it soon became obvious that disease of this structure does not present a consistent clinical picture, but varies with the anatomic and physiologic disturbances which result from the specific affection of the Meckel's diverticulum. Because of this, the diagnosis often is obscure, and many times the children had several hospital admissions before the true nature of the lesion became obvious. This was particularly true in the children with gastrointestinal tract bleeding and abdominal pain. Those lesions causing obstruction or perforation obviously resulted in operation on the first admission, but the underlying cause was

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seldom ascertained preoperatively. Because of the bizarre symptoms which these children often present, it seems worth while to suspect this anomaly whenever a child presents with the signs of intestinal obstruction, peritoneal irritation, or severe anemia.

Fifteen cases represented a problem in gastrointestinal tract bleeding. Eleven of these children had acute massive hemorrhage while in the other 4 the problem was that of severe anemia of unknown origin. All had hemoglobin levels below 10 Gm. Three-fourths of the children were under 1 year of age, a finding consistent with that reported by Gross.[2]

When ectopic gastric mucosa produces chronic ulceration and cicatrization of the ileum adjacent to a diverticulum, the symptoms are often obscure. In this situation one must be alert to fit together the syndrome of recurrent abdominal cramps associated with blood in the stool. This should result in a strong suspicion that a Meckel's diverticulum is the cause of the complaint. The cramplike pain is usually of 3 to 5 days' duration and may be associated with vomiting. This syndrome is seen at any age, varying from 4 months to 14 years in our experience. The ectopic gastric mucosa is not always associated with visible ulceration at the time of operation. The abdominal cramps may dominate the clinical picture with the child's parent being unaware of the bleeding. Examination of the stools for occult blood from time to time is indicated, for if the association of cramps and bleeding can be demonstrated the diagnosis is at hand.

It was never necessary in our cases to perform emergency laparotomy to control the intestinal bleeding of Meckel's diverticulum. Management consisted of transfusions until the hemorrhage ceased, and then complete investigation for the source before consideration was given to abdominal exploration. Since laparotomy for undiagnosed intestinal bleeding frequently results in the source being undetermined, the majority of the patients were sent home to await a second possible episode. Then, if intestinal tract bleeding recurred, exploration was performed following stabilization of the vital signs by blood replacement.

In those patients who presented with intestinal obstruction as the primary complaint, in 10 the mechanism was intussusception with a diverticulum as the lead point, and in 7 others it was a volvulus around the Meckel's diverticulum. These children were acutely ill and demanded urgent operative intervention as soon as preoperative preparation made them adequate surgical risks. It is important to note that in those cases of intussusception, two occurred in infants 4 and 6 months of age. This to us, is ample evidence that reduction of intussusception by barium enema in the infant age group is not without the possibility of overlooking a pathologic lead point. There were 5 infants and 2 children in whom obstruction was caused by a volvulus around the Meckel's diverticulum. The symptomatology in these cases did not arouse the suspicion of Meckel's diverticulum as being the causative agent of the obstruction.

In the 22 cases which we have classified under abdominal pain, there were two types: those in which there were acute episodes of pain and evidence of peritonitis at operation, and those in which there were recurrent attacks of

pain without symptoms of intestinal obstruction. There were 15 children in this latter group; the youngest was 5 years old and the mean age was 10. All of these patients were operated upon because of undiagnosed abdominal pain for which no source could be found despite intensive studies which included an intravenous pyelogram, gastrointestinal x-rays, and an electroencephalogram. Laparotomy was finally undertaken as a diagnostic procedure. There were 4 infants and 3 older children in the group with acute abdominal pain who required emergency surgical intervention. All of these had an acutely inflamed Meckel's diverticulum with perforation and peritonitis as the source of their pain.

Of the one child with the umbilical sinus, little need be said except that any time there is drainage noted from the umbilicus, patency of the omphalomesenteric duct should be suspected along with anomalies of the urachus or chronic granulomatous processes involving the umbilical arteries or vein. It is our feeling that very little preoperative investigation need be done, since the source of the drainage becomes obvious on exploration.

In the group of patients in whom an incidental diverticulectomy was performed, 2 were children with intussusception in whom the Meckel's diverticulum played no part as to the lead point. In one operation for an omphalocele, a diverticulum was noted and excised. In one child with acute appendicitis, diverticulectomy was likewise performed. Two other instances of incidental diverticulectomy occurred, once when a midgut volvulus was being reduced, and on another occasion during a pull-through procedure for Hirschsprung's disease.

OPERATIVE MANAGEMENT

We believe that the choice of operative procedure performed upon a sick child must be made as an individual decision at the time of operation. Therefore, we are purposely not attempting to advocate stereotyped operations to fit the various circumstances that might be encountered.

An intestinal resection was necessary in 12 of the 17 patients admitted with intestinal obstruction. Primary intestinal anastomosis was successfully performed in the presence of dilated intestine in all of these patients except one in whom a Mikulicz's exteriorization was selected. The presence of gangrene in three-fourths of the intestinal segments resected did not unfavorably influence the results.

In those children with abdominal pain without evidence of generalized peritonitis, diverticulectomy was possible in all instances. Those with perforation and generalized peritonitis were satisfactorily managed by diverticulectomy in 5 cases and resection and primary anastomosis of the adjacent ileum in one. The one death occurred in a moribund child with peritonitis in whom a Mikulicz's exteriorization was performed.

Diverticulectomy was performed in 9 of the 15 children with gastrointestinal tract bleeding. The adjacent ileum was removed with the diverticulum in the remaining 6. Both of these procedures were equally effective in controlling hemorrhage.

Diverticulectomy was done as an incidental procedure in the presence of such serious primary disease as midgut volvulus, aganglionic megacolon, omphalocele, and intussusception. In spite of the successful outcome of these cases, we agree with Kiesewetter's[3] opinion that incidental diverticulectomy in the presence of major surgical disease is a questionable procedure, and its use should be influenced by the seriousness of the primary lesion.

RESULTS

There were one death and 4 complications in the 61 operative procedures. The mortality occurred in a moribund child in whom peritonitis was masked by steroid therapy for Henoch's purpura. After extensive efforts to improve this child's state of shock, laparotomy revealed a gangrenous ruptured Meckel's diverticulum with generalized, purulent peritonitis. Mikulicz's exteriorization was performed on this moribund child with death ensuing from irreversible shock 2 hours after operation. The complications encountered were two eviscerations, one postoperative intestinal obstruction from adhesions, and one case of severe atelectasis. All were corrected successfully.

CONCLUSIONS

1. Meckel's diverticulum usually masquerades under a disguise which is dependent upon the particular complication present.

2. Severe complications of Meckel's diverticulum, such as acute bleeding, obstruction, and perforation with generalized peritonitis, occur most commonly in the infant.

3. Intussusception in infants is not always idiopathic but may have a Meckel's diverticulum as a lead point. Consequently, thought should be given before treating intussusception by barium enema reduction.

4. Meckel's diverticulum should be considered as the source of obscure recurrent abdominal pain in older children, particularly if gross or occult blood is found in the stool.

5. Primary anastomosis in the presence of intestinal obstruction has an excellent prognosis. However, Mikulicz's resection should be kept in mind as the operation of choice for the severely ill patient, or the child whose intestine is so edematous and friable that primary anastomosis is dangerous.

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Editorial

CONDUCTED BY I. S. RAVDIN, M.D., AND J. GARROTT ALLEN, M.D.

The Responsibility of the Doctor of Medicine in the Training of Nursing Personnel and the Governing of Nursing Care Policy in the Modern Hospital

In a recent article in a prominent Los Angeles newspaper, the following statement was attributed to the Dean of the School of Nursing of a large western university: "Here we hope to have the faculty of the School of Nursing responsible for the policy governing nursing care of patients. This is a new departure, you know, but we're sure it will work."

I would suggest that the responsibility for nursing care always has and still does rest with the medical profession and should be reaffirmed and implemented. Nevertheless, the above quoted statement by a person prominent in nursing education clearly signifies that there is a divergent point of view and attitude as to who carries the ultimate responsibility in nursing care. Such a change as is implied in the statement could only have been brought about by the fact that most members of the medical profession have been prepared to delegate, either voluntarily or involuntarily, or deliver by default such responsibility to those outside of the medical profession; specifically, educators in nursing matters.

As in the fields of hospital administration and sociomedical economic administration, doctors of medicine have, with few notable exceptions, tended to divorce themselves from close interest or supervisory roles in the field of nursing education, primarily because of the time-consuming requirements of professional scientific activities. By so divorcing themselves, however, they have abrogated their responsibility in the matter of proper nursing care, and it is the need for "properly" trained nurses which they and their patients feel is distressingly severe. It is perhaps true that part of this present need for adequate numbers of trained hospital and bedside nurses stems from the loosening of the reins of responsibility by the physicians. The reins have dropped to others who may be inadequate to respond or are insensitive to the important needs of patient and physician.

In the care of the sick patient and the study of disease and its effect upon man in modern society, there is one individual who deserves and carries the ultimate responsibility. That individual is the attending physician, the doctor. Irrespective of all ancillary aids made available to him for the diagnosis and

treatment of the problem case at hand, he, and he alone, must make the decisions which govern the welfare of his patient. It is to him that the patient turns for the answers to all facets of his medical problems, be they interpretation of laboratory tests, or the nature of the diet which he receives at the hands of the hospital dietitian, the timing of the medication administered by the staff nurse, or the items contained in the hospital bill which the patient receives.

Because his doctor does, in fact, carry this load, the patient expects that he also logically is capable of controlling all such aspects of the patient's environment which will contribute to his recovery from illness. Clearly, the doctor cannot control all of them, but he should be able to control the professional medical and nursing environment. He has been aided heretofore by many thousands of dedicated nurses, nurses who, while practicing their art, also instructed and trained student nurses to fill the need in caring for sick people.

However, there has grown up a spirit among certain individuals in nursing education which leads them to suggest that the traditional lot of the nursing profession was akin to degradation and subservience, that emancipation from the doctor should occur, and that the "new look" should encompass an elevation of the economic and social standards of nursing personnel to heights which approach the doctor of philosophy level. Rather than working "in harness" by and with the doctor's guidance in a harmonious relationship in which each recognizes and respects the other's place and capacity, the new spirit engenders the attitude that professional equality must prevail (with the patient caught between).

The time is long past in this country when anyone could justifiably look with scorn upon any such occupation, and I would suggest that this spirit which abhors the lot and status of the "old fashioned" nurse is misdirected and ill-conceived, and generated through a lack of appreciation of the need for good nursing care in the management of the sick patient.

There is no argument with those who wish to improve their social, economic, or political status; this is the prerogative of every citizen of our nation, and is to be encouraged and given every opportunity of fulfillment. There remains, notwithstanding, the need for nurses (in the true sense of the word) for the care of the sick patient. Nothing can replace the intelligent, sympathetic, courageous, sensitive, and responsive nurse, who, taking her direction from the doctor, is able to make the patient's illness a bearable one, and who does her job with the blessing of the physician to see that the patient is brought back to health.

It is patently clear that many who aspire solely to an academic hierarchy in nursing education are out of step with those who are dedicating themselves to the care of the sick in the fashion described. There may be a place for them; let them proceed with their pursuit; but let them not attempt to replace or usurp the name of the real nurse or detract from the need of the bedside nurse as the patient and the physician require it.

It is incumbent upon the medical profession and upon the responsible members of the nursing profession to see that a sufficient number of well-trained graduate nurses qualified for the registered nurse's status be trained throughout the hospitals of this country to fill the need of the sick patients, particularly for the performance of bedside nursing. The direction of policy for the care of the patient should, as it always has in the past, remain in the hands of the medical profession with the cooperative collaboration of those dedicated teachers who run the training schools of nursing.

In the finest tradition of nursing, nothing could be more honorable than to serve in the care of the sick under an organization in which humanity, high-grade intelligence, and hard work are combined under the guidance of the responsible physician such that the patients receive optimal care.

I would reject as a backward step in medical care the concept that the faculty of a school of nursing with the "new look" spirit described here be responsible for policy governing nursing care. Such policy should be, as it has been in the past and must continue to be, the purview of the medical staff.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

END RESULTS IN THE TREATMENT OF MALIGNANT MELANOMA

A LATER REPORT

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(From the Memorial Center for Cancer)

SEVEN years ago we presented a report[14] based upon experience with 1,190 cases of malignant melanoma treated and followed at the Memorial Center for Cancer, covering the period from January, 1917, through December, 1950. The 5-year definitive cure rate was therefore available for the patients treated prior to 1945 (Table I). The present series recorded in this report consists of all patients (189) with melanoma of the skin, both early and advanced, whether previously treated or not, or whether considered susceptible of cure, who applied at Memorial Hospital during the period Jan. 1, 1948, to Jan. 1, 1951. Sufficient time has now elapsed since treatment to permit comparative 5-year end result studies with the earlier group (Table III). From such data, it should be possible to determine if improvement in the methods of therapy has occurred and to accredit such betterment to certain principles and technique of therapy. The total experience to date exceeds 1,700 cases of malignant melanoma; it is hoped that the prognosis for the future patient with this neoplastic disease will continue to improve.

TABLE I. FIVE-YEAR END RESULTS IN THE TREATMENT OF MELANOMA ACCORDING TO LOCATION, 1917 THROUGH 1945

LOCATION	TOTAL CASES	DETERMINATE CASES	5-YEAR DEFINITIVE CURES	
			NUMBER	PER CENT
Total cases	744	575	123	21.4
Head and neck	173	128	23	18.0
Eye	47	35	9	25.7
Oronasal	17	11	1	9.1
Arm	58	46	8	17.4
Palm	11	8	7	87.5
Subungual	24	18	7	38.9
Leg	125	98	30	30.6
Sole	59	48	15	31.2
Trunk	162	131	18	13.7
Genitalia	31	25	4	16.0
Anorectal	16	10	0	0.0
Primary site not determined	21	17	1	5.9

From Pack, Gerber, and Scharnagel.[14]

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The term "melanoma" is used to signify the malignant tumor only. Prepubertal or juvenile melanoma is not included in this discussion or presentation of statistical data because of the disparity in clinical behavior. All tumors in this study have had histologic confirmation of the diagnosis of malignant melanoma.

PROPHYLACTIC TREATMENT

Although the prevention of malignant melanoma has no bearing on the end results of treatment of melanomas already established, its consideration here may be parenthetically inserted, in view of certain relevant facts about moles which have been established during the past decade.

Frequency of Moles.—In two separate surveys of 500 and 1,000 adult white people, the average number of moles per individual was found to be 18 and 14.6.[15] Some had hundreds of nevi; no person in these groups was without a visible mole. The frequency of the mole and the rarity of the melanoma confirm the accepted policy of not excising all moles.

Acquired or Congenital Moles.—Moles have been improperly assigned to two categories, congenital and acquired. This distinction is possibly based on the date of recognized appearance of the mole, that is, at birth or in later life. The invisibility of a nevus and its later detection after pigment is elaborated is not proof of its acquired origin. Some moles become visible as pigmented lesions when the skin is examined in a dark room with the aid of Wood's light. Nevi are probably all congenital.[13]

Age of Patients With Moles.—Many moles in infants are invisible at birth but appear later, perhaps after some exposure has exerted its melanin-provoking influence. With approaching pubescence, pre-existing moles commonly change to become larger, darker, and more elevated; other moles, invisible or faintly seen, show increased pigmentary changes. The pigmented nevus is extraordinarily sensitive to the stimulating influence of the pituitary, adrenal, and gonadal hormones. The prepubertal melanoma seldom metastasizes in our experience; rare exceptions do occur and published case reports attest to this possibility. Malignant melanomas can be avoided by the prophylactic excision of benign precursory nevi in childhood, especially those suspected of being junctional nevi or having a junctional component.[7, 8]

Occult Primary Melanoma.—It is believed that every melanoma arises from a junctional or compound nevus,[2] but the identity of a pre-existing nevus cannot always be assured, dependent as it is on the patient's awareness. In the case of melanomas in general, 60 to 75 per cent of patients reported the long antecedent presence of moles, presumably benign. In the series of 121 melanomas on the feet reported by Booher and Pack,[4] only 30 (24.8 per cent) were apparently preceded by long-standing moles of which the patients were conscious. In 3 per cent of our patients with melanomas, the primary lesion has forever remained cryptic and undetected, the diagnosis being made by microscopic study of metastases. Under these conditions the prognosis is usually fatal, although 2 patients are

alive without recurrence 6 and 18 years after surgical treatment of the metastases, during which intervals the primary melanomas have never appeared.[9] One cannot apply prophylaxis for a cancer in which the original locus remains obscure.

Regional Distribution of Moles and Melanomas.—From a study of the comparative frequency of regional distribution of moles and melanomas[15] certain important conclusions may be drawn; such as, head and neck—moles 13.2 per cent, melanomas, 28.9 per cent; upper extremity—moles 30.2 per cent, melanomas 10.9 per cent; trunk—moles 39.3 per cent, melanomas 23.6 per cent; lower extremity—moles 17.2 per cent, melanomas 29.6 per cent; foot—moles 0.3 per cent, melanomas 14.5 per cent; genitals—moles 0.1 per cent, melanomas 2.8 per cent. Moles, surgically excised and submitted for study to Drs. Allen and Spitz in the Laboratories of Pathology of the Memorial Hospital, afford a logical explanation of disparity in the regional distribution of moles and melanomas. As an example, 71.4 per cent of moles on the feet are of the junctional or compound variety, from which melanomas originate (hand—34.3 per cent) (Table II). It would be a proper prophylactic procedure to remove those moles on the feet and genitals which the experienced therapist deemed susceptible to change.

TABLE II. REGIONAL RATIOS OF MOLES AND MELANOMAS*

	MOLES (% DISTRIBUTION)	MELANOMAS (% DISTRIBUTION)	RATIO (APPROXIMATE)
Head and neck	13.2	28.9	4 to 9
Upper extremity	30.2	10.9	3 to 1
Lower extremity	17.2	29.6	3 to 5
Foot (including sole and nail bed)	0.22	14.5	1 to 48
Trunk	39.3	23.6	5 to 3
Genitals	0.1	2.8	1 to 28

*Representative regions only. Not all sites specified, for example, melanomas of feet are included under "Lower extremity."

Complexion of the Patient.—Moles and melanomas are infrequent in American Negroes and American Indians but quite common in mulattoes and mestizos. It is estimated that about 11 per cent of the American white population are blondes with fair, delicate skin and blue eyes or red- or sandy-haired people with freckled skin and hazel-blue eyes; 60 to 70 per cent of patients with malignant melanoma have this type of skin and hair.[16] All darkly pigmented moles in people of these complexions should be removed as prophylactic procedures.

Influence of Pregnancy on the Behavior of Moles.—The state of pregnancy is associated with increased pigmentation of the skin, for example, of nipple and of vulva. Moles darken during pregnancy. Melanomas develop with disconcerting frequency in the pregnant woman, three times as frequently as in nonpregnant patients, making allowance for the comparative and average number of months during which the average woman is pregnant.[18] Surgical excision of selected darkening moles during early pregnancy would seem warranted.

Role of Trauma in the Conversion of Moles to Melanomas.—It has long been asserted that moles in locations subject to irritation by belt, collar, razor, shoe, and so forth may become malignant by such physical trauma. With increasing experience, this theory is probably untenable. The benign nevus is a fairly stabile structure, whereas the melanoma is fragile, labile, vascular, and easily disrupted by slight injury. It is more probable that a bleeding ulcerated pigmented lesion, removed and found to be melanoma, was malignant prior to the injury, this accident leading to the detection of the true nature of the disease (traumatic determinism) rather than to have a bearing on the causal genesis of this cancer. Solar injury is a reasonable provocative factor because sunlight is known to stimulate melanoblastic activity, both functional and proliferative. Melanomas are more frequent in the north of Australia, that is, nearer the equator and with greater actinic exposure, than in the southern extremity of the continent.[3] Moles prone to injury should be removed not necessarily from fear of conversion to melanoma but because (a) any bleeding or ulcerated mole should be studied microscopically to ascertain if melanoma is present, and (b) trauma to an existing melanoma can hasten dissemination.

Moles Coexistent With Melanomas (Multicentric Melanoma).—Patients with proved malignant melanoma have noticed and we have observed that coexistent nevi in their skin may exhibit increased pigmentation. Excision of such moles and microscopic examination reveal that many of these lesions show evidence of activation. The modus operandi of this change has not been discovered but it is an acknowledged fact. Some patients cured of melanoma may live long enough for additional melanomas to occur in their same person. New primary melanomas can be distinguished from melanotic satellitosis, because the primary lesion can usually be traced microscopically in continuity with the superjacent or adjacent skin showing junctional changes, whereas the dermal metastases of melanoma commonly disrupt the skin. We found 16 of our first 1,250 patients (1.28 per cent) with melanoma to have multicentric lesions,[19] but this figure is probably too low because of (a) our failure to detect the primary nature of the second lesion in our beginning experience, and (b) the mortality and low curability of melanoma in the earlier years. It is wise prophylaxis to be vigilant and prompt in excising suspected moles in patients who have had melanoma.

GENERAL PRINCIPLES OF TREATMENT MELANOMA

Biopsy.—An incisional biopsy for melanoma is done only when the primary lesion is very large, ulcerating, and fungating; even then it is done with utmost gentleness. Small skin lesions suspected of being melanoma are excised in toto rather than incised.[10] The entire specimen is thus available for study with minimal trauma in its obtainment. For such small pigmented lesions the margin is sufficiently circumferential, but primary skin approximation is usually possible. The ultimate outlook is apparently not lessened by the intervening time required for the fixed tissue staining and study of the lesion.

Three-Dimensional Local Excision.—If a malignant melanoma be found, then a three-dimensional dissection should be performed widely and ruthlessly, sacrificing the skin in all directions around the tumor and deeply below the level of the fascia. The resultant large defect usually necessitates skin grafting if it is on the extremity. The skin graft should be taken from the trunk or opposite extremity, never from the ipsilateral extremity. The skin graft, if taken by the operating surgeon, should be removed and the donor site dressed before the melanoma is excised or the graft may be taken by a second surgeon working concurrently and independently. There is real hazard in the transplantation or "seeding" of melanoma cells onto the donor site in a carelessly performed operation. If the melanoma is situated on the trunk the large surgical defect may be closed by sliding skin flaps or a Z-plasty.

Excision and Dissection in Continuity (Monobloc Procedure).—If the melanomas are situated in relatively close proximity to the regional lymph nodes into which one might reasonably expect lymph-borne metastases to be deposited, such as in the upper thigh, lower abdomen, pubis, or genitals with or without metastases to the groin, or melanomas of the upper arm, pectoral, scapular, or interaxillary regions, front or back, with or without metastases to the axilla, or melanomas of the skin of the face, lower scalp, neck, and supraspinous regions with or without metastases to the cervical lymph nodes, then this neoplastic disease may lend itself quite well to a radical dissection which is referred to as a monobloc excision or excision and dissection in continuity.[20] By this procedure, a wide segment of skin is removed distal to the location of the primary melanoma, extending up to and including the skin overlying the regional lymph nodes. The skin flaps are dissected widely back, the regional lymph nodes are dissected, and the intervening fat, fascia, and lymphatic pathways are excised in continuity. The development of the widely dissected skin flaps usually permits primary wound closure, but skin grafting is added whenever necessary. This procedure is done even in the absence of palpable evidence of enlarged nodes if the location of the melanoma is such that the operation is feasible and the nodes are suspected. Unfortunately, whenever the melanoma spreads by the hematogenous route, this operation, however ably executed, will result in failure.

Amputation for Melanoma of Extremities.—The situation may exist wherein the primary malignant melanoma is situated in the skin at a remote site from the regional lymph nodes involved by metastasis; for example, in melanoma on the sole of the foot with metastases to the femoral and inguinal lymph nodes, or a melanoma occurring in the nail matrix of a finger with metastases in axillary lymph nodes. With such an enormous intervening distance between the primary melanoma and the metastases in regional nodes, it is not possible by any technical operative procedure to remove both the primary and metastatic foci with the dissection of all the intervening lymphatics between the two sites. In the dissemination of melanoma from foot to groin or hand to axilla, respectively, by way of the myriad of lymphatic vessels and their sluggish circulation, the accidental lodgment of the melanoma cells anywhere en route inevitably

would lead to local recurrence in the leg or arm. This complication has occurred frequently, for example, in patients having an amputation of a toe with groin dissection, with metastases occurring subsequently and diffusely in the skin and subcutaneous tissues of the intervening leg. Although the patient and his physician might consent immediately to such a radical operation as hip joint disarticulation for a bone sarcoma of the femur, it has been difficult to secure consent for this operation in the case of a small "black cancer" on the ankle with metastases to femoral lymph nodes, and yet the disease is as fatal as other types of cancer that present more frightening aspects. There have been, however, a few cases in our experience in which the discontinuous operation of amputation of a digit or excision and skin grafting for a melanoma of the hand or foot with independent axillary or groin dissection has resulted in 5-year definitive cures. Nevertheless, the number of these patients is so few in comparison with the large group of failures that one is reluctant to advise such conservative procedures except in aged subjects. It is probably safer for the patient who has a melanoma of the hand or foot with metastases to the axilla or groin, respectively, to submit to an amputation of the entire extremity plus dissection of the regional lymph nodes. In the lower extremities this would entail a hip joint disarticulation with dissection of the deep lymph nodes in the groin. In a comparable situation for the upper extremity, the preferable treatment would be an interscapulothoracic amputation with dissection of the lower cervical lymph nodes. In such an operation, the axilla is removed rather than dissected, and the surgeon has greater assurance of carrying the dissection superior to the upper limits of dissemination of the melanoma. Sacrifice of a limb has never been done until metastases from below the knee or elbow to femoral, inguinal, or axillary lymph nodes have been demonstrated.[11] In the lower extremity, the usual procedure was to perform a retroperitoneal iliac and obturator node dissection with hip joint disarticulation. Hemipelvectomy was performed when the supra-inguinal nodes were fixed within the pelvis and therefore not technically dissectible; in the experience reported by Booher and Pack,[4] cure by this means was achieved once, which has not been considered as criticism of the procedure but rather an admission of the fatal tardiness of its application. In the greater number of cases wherein these major exarticulations were performed, the operation was one of desperation rather than of hope, because some patients had extensively recurrent melanomas on the extremities with diffuse melanotic metastases in the tissues intervening between the site of the primary locus and the regional nodal involvement. We are still uncertain about the principles of conjoined management of melanomas of the hands and feet metastatic to the axilla and groin and will remain confused perhaps until amputation for early metastases to these nodes will be given an opportunity to prove its efficacy or futility. In a report on end results in the treatment of melanoma during the inclusive period, 1917 to 1945, Pack, Gerber, and Scharnagel[14] found a 5-year definitive cure rate after amputation to be 31.2 per cent, but the number of patients so treated was too small to be statistically significant (16 amputations with 5 cures), and the amputations were generally

not of the degree characterized as exarticulations of the limbs. In a later publication (1956) dealing with 228 major exarticulations for malignant neoplasms of the extremities, I[11] analyzed the data on these operations for 69 patients with melanoma of whom only 4 survived over 5 years without evidence of cancer. It was shown also in this report that the prognosis for patients subjected to these amputations for recurrent cancer of the extremities was 12 to 45 per cent inferior to the prognosis for patients in whom the same operations are applied as primary or initial treatment. The causes of postamputation failure in the treatment of malignant melanoma were: (a) bone and visceral involvement (lungs, liver, brain, and heart), and (b) skin recurrences in the stump and extension into superior groups of lymph nodes, pre-aortic, cervical, mediastinal, and others.

REGIONAL CONSIDERATIONS IN THE THERAPY OF MALIGNANT MELANOMA

Melanoma of the Face.—Melanomas on the exposed skin of the face are detected earlier than elsewhere with the exception of the hand. A considerable number of facial melanomas can be adequately excised without the necessity for skin grafting because of the feasibility of utilizing sliding or transposed skin flaps. The principle of excision and dissection in continuity with neck dissection cannot be applied always, but is done whenever possible, as in cases of melanomas of skin of neck, chin, lip, ear, mastoid region, and lower half of face. If the primary melanoma is sufficiently adjacent to the cervical nodes, an elective neck dissection is usually done even though no nodes are palpably suspicious. The preauricular and parotid lymph nodes may be in the drainage basin of certain melanomas requiring conjoined dissection which usually involves segmental parotidectomy (external to the facial nerve).

Of benign nevi excised, 49.4 per cent were on the head and neck, but the indications here are largely for cosmetic rather than prophylactic reasons. The occurrence of moles and melanomas on the head and neck reveals a preponderance of melanomas, almost 2 to 1 (13.2 per cent—nevi; 28.9 per cent—melanomas).[15]

Melanomas of the face and neck now offer a better prognosis than in earlier years and, in fact, better than for most other regional locations, for example:

A. *1917-1945.* 173 cases of which 128 were determinate cases with 23 cures (18 per cent) (Pack, Gerber, and Scharnagel[14]).

B. *1936-1946.* 106 cases of which 80 were determinate cases with 29 5-year cures (36 per cent) (Catlin—Head and Neck Service, Memorial Cancer Center[5]).

C. *1948-1951.* 46 cases of which 38 were determinate with a 5-year definitive cure rate of 39.5 per cent (present report).

Melanoma of the Scalp.—Malignant melanomas of the scalp have been extremely dangerous, attributed in part to its vascularity and the frequency of blood-borne metastases. Our experience has been largely limited and influenced by the fact that melanomas of the scalp usually have been recurrent at the time

of our treatment. The scalping excision should be very wide and skin grafting should always be necessary. Many of the melanomas in our personal series were situated in the retromastoid and occipital regions and were treated by excision plus unilateral neck dissection or bilateral dissection of the posterior cervical triangles.

Oronasal Melanoma.—Only 2.5 per cent of melanomas occur in the oronasal mucosa, usually on the superior or inferior alveoli or on the palate. Over 30 years ago, George F. Laidlaw[6] used selective silver staining and demonstrated the presence of melanoblasts in the normal human oral mucosa, especially on the gums. Moles are not seen; precursory lesions have not been described so prophylactic excision has not been possible. This region is seldom routinely examined. The appearance of melanin in the mouth may be of serious importance. Treatment has been by radical surgical excision. From a review of earlier publications, only three absolute cures have been reported.

Melanoma of Skin of Trunk.—The comparative incidence of moles to malignant melanomas occurring in the skin of the trunk is a ratio of approximately 5 to 3 (moles—39.3 per cent; melanomas—23.6 per cent). Regional metastases to nodes may be potentially widespread, either to groin or axilla or to both groin and axilla or to all four groups of nodes, depending on the location of the primary lesion. Melanomas of midline situation, such as on the pubis, the interscapular region, and the mid-chest, are dangerous because of the possibilities of bilateral dissemination, in which event the application of the principle of monobloc excision and dissection in continuity becomes a technically difficult problem. One patient with umbilical melanoma developed metastases to right axillary nodes 14 years after the original excision. Umbilical melanomas may extend along the urachus or ligamentum teres to implicate the urinary bladder or liver, respectively. The type of local excision again is three-dimensional with wide sacrifice of skin and fascia; the large defect can frequently be closed by a Z-plasty or the ancient sliding skin flaps devised by Celsus.

The outlook for patients with melanomas of the trunk has improved over the years:

A. *1917-1945.* 162 cases of which 131 were determinate with 18 cures (13.7 per cent) (Pack, Gerber, and Scharnagel[14]).

B. *1948-1951.* 39 cases with 31.2 definitive 5-year cures (present report).

Melanoma of the Vulva and Penis.—Of 14,609 nevi counted in adult white patients only 14 genuine pigmented moles were discovered on the vulva and penis: 0.1 per cent of all moles as compared with 2.8 per cent of 1,222 melanomas (ratio 1:28) (Pack, Lenson, and Gerber[15]). Prophylactic excision of all genital nevi should be done. Many genital moles are of the junctional type. This rule does not apply to the many pigmented spots commonly seen on the genitals and which are obviously not moles. The existence of the primary melanomas is sometimes unknown to the patient; its presence may be first

heralded by the appearance of a palpable hard inguinal node in the superomedial group. The treatment more recently adopted is a total vulvectomy (external to the hymenal orifice) in continuity with a bilateral groin dissection and a similar procedure for the rarer penile melanoma. A deep iliac and obturator lymph node dissection is indicated whenever metastases are clinically evident. Four patients of 25 determinate cases of melanoma of the female and male genitals were cured (16 per cent); none of these cures was achieved by the author.

Anorectal Melanoma.—In the report by Pack, Gerber, and Scharnagel,[14] all 19 patients with anorectal melanoma (1.6 per cent of all melanomas) succumbed to the disease. Considering the thousands of proctoscopic examinations which are done every year, it is surprising that pigmented nevi are not commonly found in the anorectal mucosa. It is seldom that they are excised and studied microscopically, an unfortunate circumstance inasmuch as it removes all opportunity for prophylaxis. Melanoblasts are of some frequency in the mucocutaneous junction. The melanomas involve the perianal skin or the mucosa within the grasp of the sphincter or in some instances are entirely internal. The earlier treatment by local dissection or perineal excision was later replaced by the classical abdominoperineal resection of Miles, which also has proved to be insufficient in view of the frequency of groin metastases. The ultimate high mortality is probably due to blood stream metastases by the portal venous system.

Malignant melanomas of the anorectal canal require a radical abdominoperineal rectal resection even more urgently than is indicated for the average adenocarcinoma of the rectum. In addition to the classical abdominoperineal rectal resection, the operation consists of a pelvic lymph node dissection and a bilateral dissection of the inguinal and femoral lymph nodes in continuity with the anus by removing a wide strip of skin and subcutaneous tissue with the fascia intervening between the groin and the perineum, the procedure being done in one continuous seance.

Subungual Melanoma.—Pigmented nevi are not so frequently encountered in the nail bed and, when seen, should be surgically excised in their entirety in order to be available for microscopic study; in our experience the melanoma occurs much more frequently in the nail bed than does the pigmented nevus. This advice is based on the clinical difficulty in establishing the differential diagnosis between malignant melanoma and such benign lesions as subungual hematoma, subungual hyperkeratoses, and chronic paronychial infections. Many of the subungual melanomas are nonpigmented and, because of this, the majority of patients have had partial or complete removal of the nail bed with such traumatic procedures as curettage or partial excision before the true nature of the disease is recognized. In an earlier group, 14 of 16 melanomas of the nail bed had been curetted elsewhere.[12] The suffusion of the melanotic pigment may extend far beyond the nail bed, and this characteristic halo of pigment at the tip of the finger and along the lateral aspects of the nail surface often is pathognomonic in the establishment of a correct diagnosis.

TABLE III. FIVE-YEAR END RESULTS IN MELANOMA OF THE SKIN (MEMORIAL CANCER CENTER)*

	HEAD AND NECK	UPPER EXTREMITY	TRUNK	LOWER EXTREMITY	GENERALIZED	TOTAL
Total Experience						
Total number of patients applying	46	33	39	70	1	189
Indeterminate Cases						
Consultation only—treatment not required	1	—	1	2	—	4
Refused proffered treatment or palliative care	2	1	1	2	—	6
Lost track of without recurrence following treatment	3	1	1	3	—	8
Dead from other causes without recurrence	1	1	—	—	—	2
Applied following successful treatment elsewhere with no recurrence on admission or later	1	8	4	18	—	31
Total number of indeterminate cases	8	11	7	25	—	51
Determinate Cases						
Total number of determinate cases	38	22	32	45	1	138
Failures						
Dead as a result of cancer or its treatment	19	13	20	24	1	77
Living with cancer present	1	—	—	1	—	2
Dead of other causes with cancer present	—	—	—	—	—	—
Lost track of with cancer present	3	1	2	1	—	7
Untreated failures (considered to be too advanced for treatment)	—	—	—	—	—	—
Total number of failures	23	14	22	26	1	86
Successful Results						
Total number of patients known to be alive and without evidence of melanoma at 5 years following admission	15	8	10	19	0	52
Net 5-Year End Results (per cent)						
Total number of successful results divided by the number of determinate cases	39.5	36.4	31.2	42.2	0	37.7
Five-Year Survival Rate (successful results plus living with cancer present divided by the number of determinate cases, per cent)	42.1	36.4	31.2	44.4	0	39.1

Analyses by Mary C. MacDonald, formerly Biometrician, Memorial Cancer Center, New York, N. Y.

*This series consists of the cases of all patients with melanoma of the skin, both early and advanced, whether previously treated or not, or whether considered susceptible of cure, who applied at Memorial Hospital during the period Jan. 1, 1948, to Jan. 1, 1951.

The frequency of subungual melanoma (the melanotic whitlow of Jonathan Hutchinson) is in the neighborhood of 3 to 3.5 per cent of all melanomas (Pack and Adair—16 of 477 cases, 3.4 per cent, 1939,[12] and Pack, Gerber, and Scharnagel—35 of 1,190 cases, 2.9 per cent, 1952[14]). In the large collective series, subungual melanomas occurred almost twice as often on the toes as on the fingers, but in a more recent study by Booher and Pack of 151 melanomas of the hands and feet during the years 1935 to 1950, inclusive, there were 29 subungual melanomas of which 13 were on the fingers and 16 on the toes. The subungual melanomas comprised 44.8 per cent of all melanomas of the hand and 13.1 per cent of all melanomas of the feet.

The average patient is willing to give consent for the sacrifice of a digit by amputation, which he will not so readily do for melanomas involving a major extremity. The amputation should usually be above the level of the metacarpophalangeal joint for better functional, cosmetic, and curative results. In two series of cases the results were as follows:

A. Thirty-five cases treated prior to 1952, 24 prior to 1946 of which 18 were determinate cases available for estimates of cure. Seven of these 18 patients (38.9 per cent) were cured.

B. Twenty-nine cases treated between 1935 and 1950, an absolute cure rate of 20.7 per cent.[4]

Melanoma of the Hands and Feet.—Of moles excised from the feet (which do not include nontumorous pigment spots) the junctional nevi comprised 7.1 per cent and the compound nevi 64.3 per cent, or a total of 71.4 per cent which are potentially capable at least of becoming malignant. Of moles excised from the hands, the junctional nevi comprised 6.2 per cent and the compound nevi 28.1 per cent, or a total of 34.3 per cent which are potentially capable of becoming malignant. The microscopic classification of these moles was made by Drs. Arthur C. Allen and Sophie Spitz, pathologists, on material furnished from the Mixed Tumor Service of the Memorial Hospital.

Booher and Pack[4] analyzed all malignant melanomas of the hands and feet at the Memorial Cancer Center between 1935 and 1950, inclusive. The statistical data were summarized as follows:

> In the 16-year period, 16.5 per cent of all malignant melanomas were on the hands and feet. Of these 151 melanomas, 29 were on the hands and 122 were on the feet. The patients were aware of a preexisting mole on the foot in 24.8 per cent of those having melanoma. (This awareness was present in 60 to 75 per cent of patients having melanoma in other skin sites.) In 32 (26.2 per cent) melanomas of the foot local surgical measures were employed with a 5-year definitive cure rate of 34.4 per cent. The 5-year definitive cure rate for all melanomas of the feet was 25.3 per cent. Elective groin dissections without clinical evidence of metastases but in which on microscopic study the nodes were found to contain metastases yielded a 5-year definitive cure rate of 20 per cent. In elective groin dissections without clinical evidence of metastases confirmed on microscopic study, the 5-year definitive cure rate was 40 per cent. For patients with malignant melanomas of the feet having simultaneous nodal metastases in

the groin, the 5-year definitive cure rate was only 12 per cent. Of all patients undergoing surgical treatment for malignant melanoma of the feet, 16.5 per cent subsequently had either local recurrence on the feet or widespread dissemination throughout the leg. Of all patients having groin dissection for malignant melanoma, 14 of the 56 (25 per cent) had diffuse recurrence in the extremity or in the scar of the groin dissection. In a consideration of the influence of the size of the primary melanoma on the cure rate, the 5-year definitive survivals in comparison with the diameters of the primary melanomas were as follows: 1 cm., 29.4 per cent; 1 to 2 cm., 20.7 per cent; 2 to 3 cm., 22 per cent; 3 to 4 cm., 18.1 per cent; and 4 to 5 cm., 10 per cent. The total 5-year definitive cure rate for melanomas of the hand was 40 per cent. The 5-year definitive cure rate for melanomas of the hand metastatic to the axilla was 16.6 per cent.

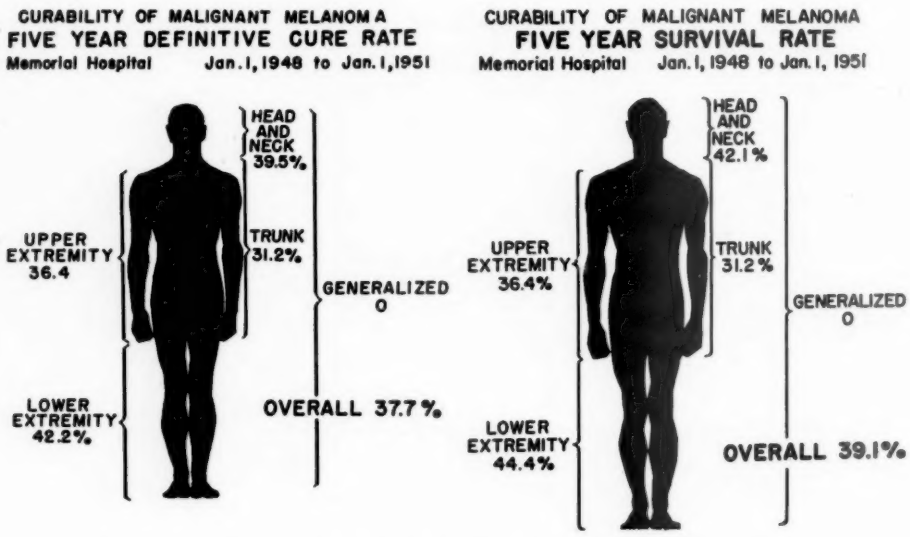

Fig. 1.—Survival rate and cure rate for malignant melanoma.

SUMMARY OF IMPROVEMENT IN END RESULTS FOR MELANOMA

It has been possible to trace the evolution in therapy of malignant melanoma in one institution, the Memorial Hospital, through a series of end result studies encompassing about 35 years of experience.

1. In 1936, 400 cases of melanoma were reported by Adair.[1] Of these, 155 were primary and 245 were recurrent melanomas. Only 105 were in the operable category (26 per cent), indicating that only 1 in 4 patients came at a time when operative removal was possible. Of the total 267 melanomas treated prior to 1931, that is, determinate cases available for 5-year analysis, 33 (12 per cent) were cured.

2. In 1947, 862 cases of melanoma were reported by Pack, Perzik, and Scharnagel.[17] Of these, 595 were deemed suitable for determination of 5-year end results. Radiation therapy yielded no cures. Surgical treatment resulted in 38.4 per cent 3-year cures, and 17.7 per cent 5-year cures in those patients

whose melanomas were localized without regional node involvement at the time of treatment. Surgical treatment of melanomas, metastatic to regional lymph nodes, resulted in 18.7 per cent 3-year cures and 15.6 per cent 5-year cures.

3. In 1952, 1,190 cases of melanoma were reported by Pack, Gerber, and Scharnagel.[14] Of these, 744 were seen prior to 1946, of which 575 were determinate cases available for 5-year end result analyses. The over-all definitive 5-year cure rate as of Jan. 1, 1951, was 123 cases (21.4 per cent). One hundred and fifty-one melanomas (26.7 per cent) were inoperable at the initial visit. An improper delay after excisional biopsy reduced the 5-year cures from 39.9 to 17 per cent. The 5-year definitive cure rate for melanomas without regional node metastases at the time of treatment was 40.5 per cent; this salvage was reduced sharply when lymphatic metastases were present to 14.1 per cent.

4. In the present report, a study of the end results of treatment of melanoma during a later 3-year period is compared with these earlier accomplishments. This reported 5-year survival rate (successful results plus living with cancer present, divided by number of determinate cases) amounted to 39.1 per cent. The 5-year definitive cure rate (all successful) was 37.7 per cent. In comparing the collective end results of earlier years with this present series on the basis of primary location, the following interesting data are noted:

	Prior to 1946	*Present*
A. Melanomas of head and neck	18.0%	39.5%
B. Melanomas of trunk	13.7%	31.2%
C. Melanomas of lower extremity	30.6%	42.4%
D. Total experience	21.4%	37.7%

5. This improvement can probably be attributed to the following causes: (A) abandonment of radiation therapy as a primary therapeutic discipline, (B) education of lay public and medical profession about the hazards of certain pigmented skin lesions, resulting in earlier diagnoses, (C) institution of surgical treatment at a time when the primary melanoma often remains localized, and (D) more adequate surgical procedures for melanomas both local and metastatic to regional nodes based on the principles previously stated.

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Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

INDICATIONS FOR OPERATION FOR ABDOMINAL TRAUMA

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THE early diagnosis and management of abdominal trauma is a most rigid test of the surgeon's diagnostic ability and clinical judgment. In spite of experience and great care, error in the accurate appraisal of clinical manifestations is frequently made. An acceptable degree of accuracy in diagnosis is accomplished only by frequent examinations and by a policy of "wait and see"; yet to wait too long may cost the patient his chance for survival and surgical cure. Mortality and morbidity increase sharply with the passage of time and the chance for cure may lie in the narrow space of a few hours.

NONPENETRATING WOUNDS

Diagnostic difficulties are greatest in blunt wounds because of (a) the absence of external evidence of injury is deceptive, (b) the high frequency of associated injuries or an unconscious patient, and (c) the fact that trivial injuries may rupture bowel or spleen. Cottrell[1] reviewed 800 cases in the literature and noted that two-thirds were associated with other injuries, especially fractures of the thoracic cage. The organs most frequently damaged were the kidneys (28 per cent), the spleen (25 per cent), the liver (18 per cent), and the gastrointestinal tract (10 per cent). The over-all mortality for such wounds is generally reported as approximately 20 per cent.[2, 3]

A severe blow on the abdomen causes enough disturbance to the nervous system to produce an initial period of collapse after injury. About 70 per cent of patients manifest a shocklike state without visceral injury and recover promptly. Immediate laparotomy is therefore seldom advisable. However, an apparent recovery cannot be definitely established until all clinical manifestations have been carefully evaluated. One of the chief difficulties in early diagnosis is the fact that intra-abdominal visceral injury does not produce signs for several hours. For these reasons it is important that the patient be examined by the same physician at frequent intervals. This does not mean one can wait 12 hours or until the following day.

During this period of initial observation, blood is given according to the patient's needs. An intranasal gastric suction tube is inserted and the contents are examined for blood. The tube is left in, a catheter is inserted into the bladder, and a supine and upright x-ray film of the abdomen are obtained.

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It is helpful in diagnosis to try to determine whether the dominant clinical signs are due to hemorrhage or peritonitis. Although free intraperitoneal air is pathognomonic of a ruptured hollow viscus and subsequent peritonitis, absence on the plain film does not rule out such a rupture.

The presence of tenderness, rebound tenderness, muscle spasm, and absent bowel sounds indicate peritoneal irritation. The onset may be sudden, as after spillage of colon or stomach contents or bile; it may be slow as after rupture of the duodenum or small bowel. The presence of persistent tenderness, especially if localized, is extremely important.

A confusing condition which occurs in 60 per cent of cases without intra-abdominal injury is reflex adynamic ileus. This can follow retroperitoneal or spinal injury or may be a manifestation of peritonitis. Adynamic ileus following severe trauma differs from that caused by peritonitis by its quick response to supportive treatment, normal pulse, and absence of specific tenderness.

Approximately two-thirds of patients with blunt abdominal wounds suffer either gradual or massive blood loss. Estimation of blood loss based on serial hemoglobin and hematocrit readings is fairly accurate from a practical standpoint, provided the patient is well hydrated. Blood volume studies made with radioactive phosphorus are exact but in the presence of active bleeding the values must still be correlated with the clinical picture. In the presence of definite intra-abdominal bleeding, an early effort is made to determine the amount and rate of loss because this is directly related to the need for operation. For example, blood loss that exceeds 500 c.c. per 8 hours requires operative intervention.

Diagnostic abdominal paracentesis is helpful to establish hemorrhage as a definite factor; in fact, the chief indication for this clinical tool is the patient with multiple injuries when these complications might mask the intra-abdominal loss of blood. The procedure can be carried out at the bedside. If bleeding is present it has an accuracy of approximately 75 per cent. It is a safe procedure and there is general agreement that no serious complications have ever followed it. Although a positive tap is helpful, a negative tap does not rule out intra-abdominal injury and therefore must always be used with other methods of diagnosis. It is merely one test in evaluating the whole clinical picture.[4]

Indications for Laparotomy.—Although it is helpful to know the exact diagnosis prior to operation, this is not nearly as important as reaching the correct decision regarding the need for operation. A specific diagnosis is desirable because, for example, in splenic rupture it directly affects the placing of the abdominal incision.

Absolute indications for laparotomy are: (1) pneumoperitoneum, (2) abdominal paracentesis yields blood (if associated with signs of active bleeding), and (3) recovery from shock following which the pulse rate slowly increases, blood pressure is lower than normal, and there is clinical evidence of hemorrhage. The clinical picture of progressive collapse after initial recovery is significant since it cannot be ascribed to the shock of injury.

Relative indications for laparotomy are: (1) persistent and unexplained abdominal pain and tenderness, (2) gradually increasing distention, loss of bowel sounds, and rising pulse, and (3) persistent and unexplained anemia following an abdominal injury.

The exact hour for operation depends upon the response of the patient to replacement therapy; those who remain stabilized are the best candidates. Occasionally with the use of much blood, an operation can be done in the presence of persistent shock with an occasional good result, although such situations are usually hopeless.

Rupture of the Spleen.—Rupture of the spleen is the commonest major injury that requires operation. Injury to the liver is about equally as common but the bleeding may stop whereas even small tears of the spleen continue to bleed. There are several causes for delays and errors in diagnosis of rupture of the spleen, the most important of these being failure to realize that there are variations in splenic rupture which produce marked variations in clinical signs. Trivial accidents may rupture the spleen, especially in children because of the resiliency of the rib cage. The presence of fractured ribs on the left should alert the surgeon to the possibility of splenic rupture rather than divert his attention from it. Most important is to realize that splenic rupture falls into three types, each of which produces a different clinical picture.

Classic rupture of the spleen produces gross free bleeding in the peritoneal cavity with a typical picture of abdominal pain, tenderness, and evidence of internal hemorrhage. At first bowel sounds are normal and abdominal tenderness is localized to the left upper quadrant but, as bleeding progresses and the escaping blood causes peritoneal irritation, the tenderness becomes diffuse with diminished bowel sounds and a rapid pulse. Left shoulder pain is common. Adynamic ileus is common due to the irritating action of the blood. Clinical manifestations of marked blood loss are obvious and substantiated by laboratory evidence.

Subcapsular or retroperitoneal rupture confines the blood to the left upper quadrant and away from the free peritoneal cavity. Pain and tenderness may be absent or moderate and localized to the left upper quadrant of the abdomen. In such cases persistent unexplained anemia may be the most prominent symptom.

Delayed rupture of the spleen may follow days or weeks after the primary injury. There may be slight leakage into the peritoneal cavity during this time until suddenly the capsule tears and massive hemorrhage occurs. The final clinical picture is the same as classic rupture of the spleen, but failure to elicit a history of abdominal trauma may result in delayed diagnosis.

Although the x-ray is seldom specific in diagnosis of a ruptured spleen, it frequently substantiates a clinical impression and makes diagnosis possible. In approximately two-thirds of the cases, one or more of the following findings will be noted: (1) an opacity in the left upper quadrant of a plain film of the abdomen associated with absence of the splenic edge, (2) elevation of the left

diaphragm or fluoroscopic evidence of limitation of motion, (3) displacement of the gastric air bubble to the right with the patient in the upright position (the greater curvature may be serrated due to gravitation of blood into the gastrosplenic ligaments), and (4) displacement of the splenic flexure of the colon downward as noted by either the gas pattern of the colon or by barium enema.

Rupture of the Liver.—Associated injuries are somewhat more common in rupture of the liver because the force of the blow necessary to rupture the liver is greater than that in rupture of the spleen. The most frequent associated injury involves the right kidney or fractures of the right ribs. Clinical signs of rupture of the liver are dependent almost entirely upon internal hemorrhage. The bleeding may be acute and massive, without remission and followed by progressive shock or a series of smaller hemorrhages which at any time can become acute. Unlike the spleen, the bleeding may stop spontaneously. Pain in the right upper quadrant made worse on deep respiration with occasional radiation to the right shoulder is noted as a result of diaphragmatic irritation. Needle aspiration of blood from the abdomen establishes the diagnosis. Such aspiration is particularly valuable in differentiating multiple fractures with hemothorax and shock from ruptured liver.

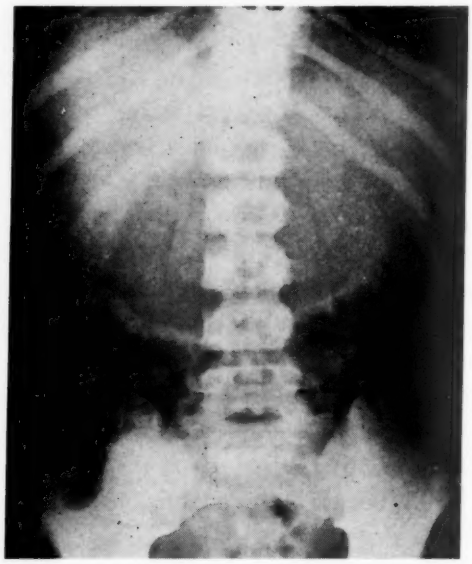
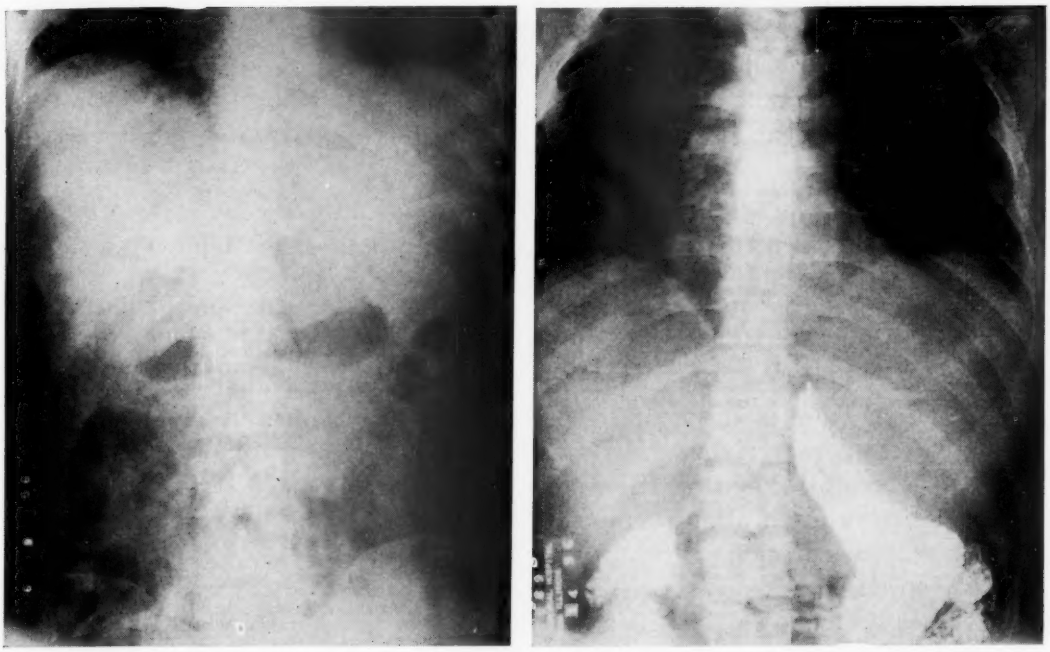


Fig. 1.—Serration of greater curvature of stomach by splenic hematoma. Child, 11, run over by tractor. Hematocrit 30, no hypotension but abdominal pain and left upper quadrant tenderness. Plain film shows marked gastrectasis and serration of greater curvature of stomach due to dissection of hematoma. (Requarth, Wm., Acute Abdomen, ed. 2, Chicago, 1958, Yearbook Publishers, Inc.)

Rupture of the Duodenum.—Rupture of the duodenum is a lethal and deceptive injury chiefly because the rupture is retroperitoneal and no contents reach the peritoneal cavity early to produce prominent signs. Symptoms at first are minimal but as extravasation of duodenal contents into the retroperitoneal tissues progresses abdominal pain, tenderness, rigidity, and low grade fever appear. There may be a period of brief shock followed by recovery and later by the gradual onset of peritonitis. During this recovery phase,



A. *B.*

Fig. 2.—Displacement of stomach by splenic hematoma. Man 31, admitted after auto accident with severe left upper quadrant pain and muscle spasm, slight diffuse abdominal tenderness, hematocrit 39. Findings attributed to fractured ribs. *A*, Plain film shows opacity in left upper quadrant with downward displacement of gastric air bubble. *B*, Confirmation by barium swallow made diagnosis of ruptured spleen.

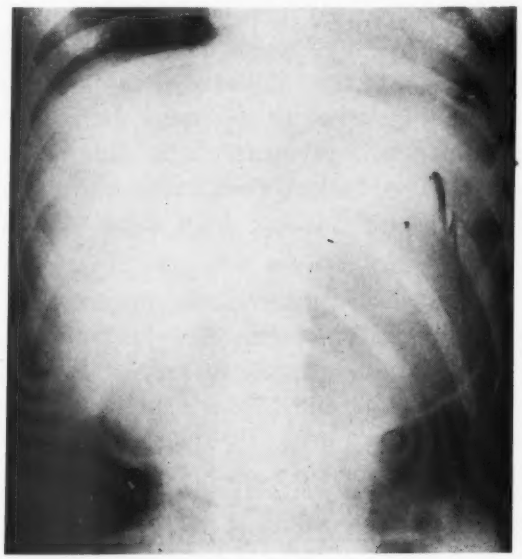


Fig. 3.—Gastrectasis and right upper quadrant density associated with rupture of liver. Child, struck by auto while riding bicycle. Admitted in shock, blood pressure 80/ ?, pulse 30, hematocrit 38, diffuse abdominal tenderness. Plain film shows opacity in right upper quadrant, fracture of right ninth rib, and dilatation of stomach. Gastrectasis is usually indicative of intra-abdominal injury. Abdominal paracentesis yielded blood.

bowel sounds are normal or only slightly decreased and the patient is usually ambulatory. The most consistent early finding is persistent deep tenderness. The x-ray itself is seldom helpful. Occasionally escaping air will outline the kidneys or there will be obliteration of the right psoas shadow. Injuries to the pancreas are frequently associated and may produce an elevation of the blood serum amylase.[5]

Rupture of the Intestine.—Rupture of the intestine occurs more often as the result of a sharp thrust, such as a kick by an animal or following a "run-over" accident in children. Clinical manifestations may be delayed because the opening is small, plugged by mucosa, or spillage is kept localized by the normal walling off process of the body. If the perforation is large or if the colon is perforated the onset of peritonitis is not delayed, and symptoms appear early. Often there is early mild shock with low blood pressure followed by a period of temporary recovery. Bowel sounds disappear with the rising pulse and white count. Pneumoperitoneum is present in about one-half of patients. It is seen more often after perforation of the upper small bowel or colon. An important consideration in rupture of the bowel is that the initial blow need not be especially strong, if it is aimed in just the right direction the intestine will be perforated. This discrepancy between the force of blow and the serious nature of the injury encourages delayed diagnosis.

Rupture of the Kidney.—Damage to the kidney is the most common visceral injury but the majority recover without operation. Pain and muscle spasm in the flank plus hematuria and fracture of one or more of the lower ribs is usually sufficient to suspect the diagnosis. Appraisal of the damage and the decision for or against operation is much more difficult. Excretory urograms are unreliable the first 24 hours since they normally show nonfunction even without damage. Retrograde pyelography, when possible, will show the extent of damage to the kidney pelvis. If the condition of the patient at first is good but later deteriorates with falling pressure, transfusions should be given and the degree of injury determined by pyelography. If this is normal, it is still best to delay operation and continue transfusions and observe since most will recover. When pyelograms reveal severe damage with signs of progressive blood loss, nephrectomy is indicated.

Rupture of the Bladder.—Rupture of the urinary bladder almost always occurs as a complication of fractures of the bony pelvis. The bladder should be emptied by catheter in every case of pelvic fracture involving the bones of the pubic region. If nothing is obtained but a little watery or clotted blood, bladder rupture is almost a certainty. If there is a normal amount of urine, even though bloody, the bladder may only be contused or there may be an injury to the upper urinary tract and in such case an indwelling catheter is all that is necessary. Approximately 15 per cent of bladder ruptures are intraperitoneal, with abdominal pain and tenderness and later a progressive ileus with evidence of peritonitis. Occasionally tenderness is mild and not well localized. In general, intraperitoneal rupture is tolerated better than retroperitoneal extravasation. In the latter instance, which is the most common type

of bladder rupture, symptoms are obscure until extensive extravasation has occurred with marked lower abdominal pain, tenderness, and rigidity. A cystogram made after the injection of Diodrast shows diffusion of the dye into the extravesicle tissues and makes the diagnosis.

PENETRATING WOUNDS OF THE ABDOMEN

Whereas diagnosis and the decision as to need for celiotomy is most important for a blunt wound, the problem faced in a penetrating wound is to determine if the abdominal cavity has been penetrated and if so, what intra-abdominal structure has been injured. In addition, the magnitude of blood loss in such wounds can be extreme. Although associated wounds may be present, with few exceptions the definitive treatment of a penetrating wound takes precedence over all else. The time relationship between injury and surgical treatment has a more direct relationship to mortality and morbidity than in any other surgical condition. There are no insignificant penetrating wounds of the abdomen. The following diagnostic procedures are recommended: (1) obtain a base line for subsequent blood changes as the result of hemorrhage (hemoglobin, hematocrit, blood volume), (2) intranasal gastric suction, (3) catheterization, (4) digital examination of the rectum for blood, and (5) obtain upright and supine x-ray films for pneumoperitoneum and for localization of the missile if the wound is gunshot.

Knife Wounds.—Unless the viscera are fixed, they tend to slide away from the advancing point of the knife and are often not penetrated. However, it is not possible to determine if a viscus has been penetrated by probing the wound. In addition, probing gives unreliable information and, owing to overriding of the layers of the abdominal wall, one may decide incorrectly that the wound is superficial. A wound is diagnosed as superficial only if intact peritoneum is demonstrated in the operating room.

Presumptive evidence of penetration of a viscus are: (1) abdominal tenderness and rebound tenderness, and (2) increasing pulse rate, decreasing blood pressure, and evidence of internal hemorrhage.

Obvious evidence of penetration are: (1) pneumoperitoneum, (2) discharge of intestinal contents from the wound, (3) recovery of blood from the stomach or bladder, (4) rapid deterioration of the patient's condition, and (5) recovery of blood on needle aspiration of the abdomen.

Gunshot Wounds.—Unlike knife wounds, in which viscera slip away from the path of the knife, a bullet rips through the abdomen and seriously damages all structures in its path. Massive contamination and serious hemorrhage frequently result. An unrelenting type of shock that is difficult to correct is not uncommon because of extreme blood loss. In such cases it is best not to attempt to replace blood prior to operation but to do it along with surgery. The mortality is high and directly related to the interval of time between injury and operation. This time factor is of extreme importance in the successful treatment of gunshot wounds.

Diagnostic effort is directed toward determining the exact course of the missile rather than weighing the evidence of penetration since, if there is any possibility of penetration, celiotomy is mandatory. The bullet usually moves straight through the abdomen unless deflected by bone. If there is no wound of exit, anteroposterior and lateral x-ray films are made to locate it. It is often possible to determine approximately what structures are injured after the path of the bullet has been defined. Posture of the patient at the time of shooting is important in considering the course of the bullet.

A most important error is failure to examine the rectum. Injuries of the rectum should be suspected in all wounds of the lower abdomen, buttock, sacrum, and hip. If there is a possibility of injury to the rectum and there is no blood on the finger after rectal examination, a proctoscopy should be done.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

A VESALIAN WOODCUT OF THE ESOPHAGUS AND STOMACH

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THE avalanche of medical and surgical knowledge, which has steadily been gaining momentum since the sixteenth century can, in part, be traced to Vesalius. It was the widespread acceptance of his work which released the minds of men from the anatomic misconceptions inherited from antiquity. His teachings formed the basis of the structural concept of normal and diseased states. Although the emphasis in the approach to the study of pathologic conditions has shifted somewhat since the days of Vesalius, no point of view has been as revolutionary, or as fruitful, as the anatomic approach. Until the true structure of the body was known, there was no possible scientific study of physiology and pathology. It is thus evident that a study of the evolution of any phase of our knowledge of a disease, or its treatment, must give due consideration to Vesalius' contributions. It is to those who may wish to study the role he played in our understanding of the esophagus and stomach that the discussion of this illustration is devoted (Fig. 1).

The woodcut referred to herein can be found in the Fifth Book *(Tabulae Libri Quinti: Organis Nutritioni Quae Cibo Potuqu Fit . . .)* of *De Humani Corporis Fabrica (Libri Septum)*. The latter was first published in 1543. A second edition, with an improved text, appeared in 1555.

The history of the woodcuts is a fascinating one. The drawings for the wood blocks were undoubtedly done by Jan Stephan van Calcar, a countryman of Vesalius and a pupil of Titian. Most of the blocks were cut in Venice at Vesalius' own expense. In August, 1542, they were sent to Basel for the publication of his book by the printer Johannes Oporinus. At the time of Vesalius' death in 1564, the blocks were taken over by his heirs.[2] According to Saunders and O'Malley, it appears that after Oporinus' death, the woodcuts may have been acquired by the Froben family and were passed on to Ludwig König, successor to the Frobens when they went out of the printing business in 1603.[5] Andreas Maschenbauer, a printer of Augsburg, purchased the wood blocks and in 1706, and again in 1723, published some of them, as the work of Titian, for the use of artists and sculptors. For a while the wood

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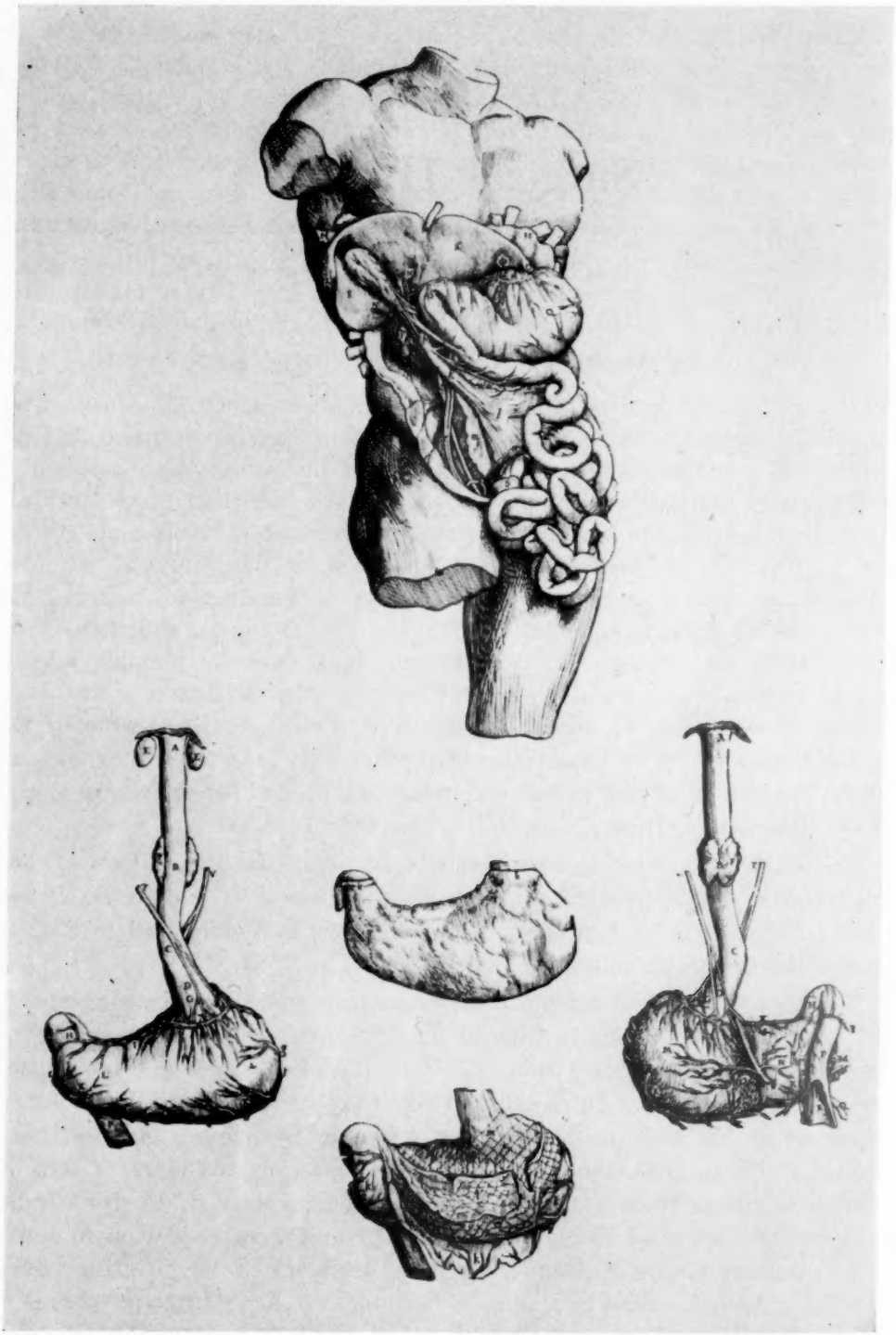

Fig. 1.—Photograph of the Vesalian woodcut which hangs in the Library of the Department of Surgery, University of Minnesota. It was obtained from the original wood blocks at the time the *Icones Anatomicae* was published in 1934.

blocks were lost but in 1777 they were rediscovered by the physician von Woltter who entrusted them to the Bavarian anatomist and surgeon, H. P. Leveling of Ingolstadt. In 1800 the library which contained the wood blocks was transferred, with the university, to Landshut in order to avoid Napoleon's invading forces. In 1826 there was another move, this time to Munich. In 1893, during the course of an inventory, the librarian of the University of Munich, Dr. Hans Schnorr von Carolsfeld, discovered some of them. In 1932, Dr. Samuel W. Lambert of New York found the remainder of the wood blocks. Immediately following this, the Bremer Presse, in association with the University of Munich, printed them under the sponsorship of the New York Academy of Medicine. No changes or improvements were made in any of the original blocks. This illustration (Fig. 1) comes from one of the imprints made from the then 391-year-old wood block. The woodcut is the property of Dr. Owen H. Wangensteen and hangs in the Library of the Department of Surgery, University of Minnesota. The entire collection of woodcuts appeared in 1934 as the *Icones Anatomicae of Andreas Vesalius.* The bombings of Munich during World War II were responsible for the ultimate loss of the original wood blocks.

In addition to the text of *De Humani Corporis Fabrica,* Vesalius prepared extensive annotations to the illustrations which he called the "characterum indices" (index of characters). He then devised a complex system of cross references for the text, the annotations, and the illustrations. This is explained in a letter to the printer.[5] The numbers of the figures were placed along the margin of the plate. The five figures depicted in this illustration bear the following numbers: 12, 14, 15, 16, and 17. Fig. 12 designates the drawing of the torso. The fourteenth figure is on the left lower side of the illustration. It is an anterior view of the esophagus and stomach (Fig. 2). The posterior aspect of the same specimen is depicted in Vesalius' Fig. 15 on the right lower side of the plate (Fig. 3). Fig. 16 is the uppermost picture of the stomach lying between Figs. 14 and 15. Vesalius' Fig. 17 is below Fig. 16 (Fig. 4). The following is taken from Saunders and O'Malley's[5] translation of parts of the "characterum indices" (brackets are mine).

> The twelfth figure of the fifth book which immediately follows the preceding complete figure in the sequence of dissection. In it the peritoneum has been dissected away, the omentum removed, and we have also fractured some of the ribs so that the entire hollow of the liver could be drawn more conveniently. Then the orifices of the stomach are seen since it, as well as the intestine, has been pushed down to the left in order to bring into view part of the mesentery, the arrangement of the portal vein in it and especially the insertion of the biliary passage into the intestine....
>
> The fourteenth figure of the fifth book [Fig. 2] represents the anterior aspect of the entire stomach and esophagus [ventriculi et stomachi], together with the veins, arteries, and nerves inserted into the stomach. [*E* represents] two tonsils which lie not far from that aspect of the esophagus extending into the oral cavity. [*F* is a glandular body] not infrequently attached to the esophagus where it

rests on the body of the fifth thoracic vertebra. [*T* and *V* are the vagi. *d* is the coronary vein. *e* denotes the gastric vessels. *g* is the short gastrics. *f* and *c* are the gastroepiploics.]

In this figure [Fig. 4] we have freed the stomach from the esophagus and intestines and then turned it inside out so that the internal aspect of the stomach, or the surface surrounding the food and drink, come into view. Here the posterior part of the stomach is encountered but not as in the subsequent or fourteenth figure, the anterior.

The fifteenth figure of the fifth book [Fig. 3] exhibits the posterior surface of the entire stomach and esophagus.

The present figure [Fig. 4] shows the arrangement number and nature of the coats of the stomach as far as it is possible to follow them in a picture. [*k* is the serosa, *l* the muscularis, and *m* the submucosa.]

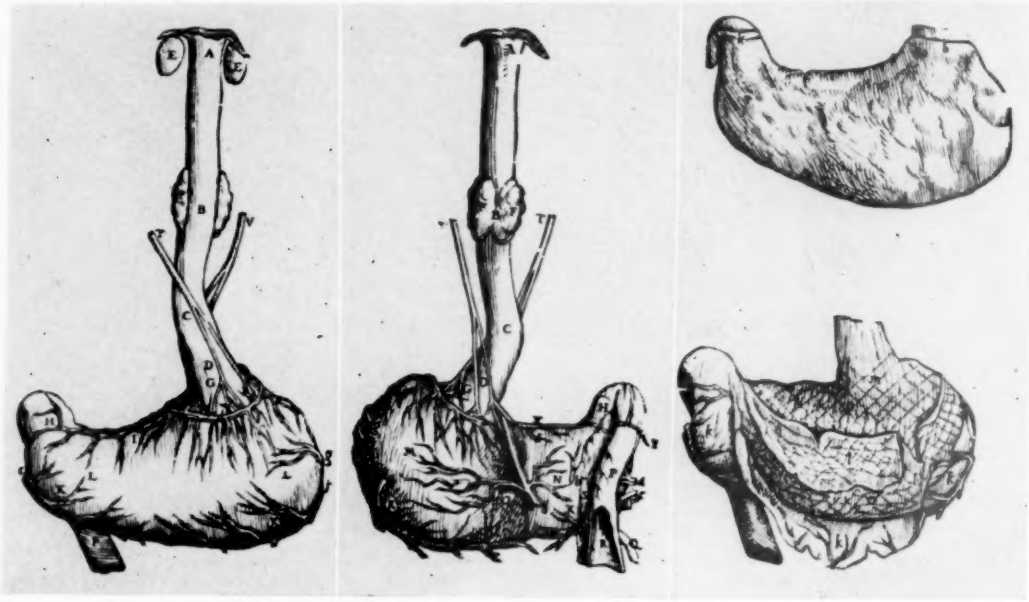

Fig. 2.—Vesalius' Fig. 14. Anterior aspect of esophagus and stomach. *E*, tonsils; *F*, corpus glandulosum; *T* and *V*, vagi; *d*, coronary vein; *e*, gastric vessels; *g*, short gastrics; *f* and *c*, gastroepiploic vessels.

Fig. 3.—Vesalius' Fig. 15. Posterior aspect of esophagus and stomach. See legend for Fig. 2.

Fig. 4.—Vesalius' Figs. 16 (*upper*) and 17 (*lower*) which represent the mucosal surface and the walls of the stomach, respectively. *k*, serosa; *l*, muscularis; *m*, submucosa.

It should be noted that Vesalius used the terms "ventriculus et stomachus" for stomach and esophagus. By "stomachus" Vesalius meant the pharynx and esophagus, as one organ which began at the isthmus faucium (*A* in Figs. 2 and 3) and ended at the "ventriculi superius orificium," the superior orifice of the stomach or the cardia.[1] However, reference to the figures shows that little, if any, of the pharynx is depicted. The "tonsillae" most probably represent the palatine tonsils which have been displaced during the course of the dissection. No explanation can be given to account for the presence of the "corpus glandulosum." Holl's paper on these glands of the "stomachus" is perhaps the best exposition of the problem.[1] The glands are undoubtedly lymph nodes. Holl himself dissected human and animal cadavers in an attempt

to find what it was that Vesalius had used as their prototype. It is also disconcerting to note that Vesalius refers to them as being frequently encountered. Vesalius thought these "glands" secreted a fluid which contributed to the saliva and moistened the "stomachus." He mentions nothing of the ducts through which the secretions would flow.

The significance of the use of cross-hatchings in Fig. 17 (Fig. 4) to depict the coats of the stomach is most interesting. According to the tenets of the humoral doctrine, the straight, oblique, and transverse fibers which made up the coats of the organs and vessels determined that organ's ability to attract and retain nourishment. The arrangement of the "fibers" (the smooth muscle layers) of the stomach was thought to substantiate this concept in that the longitudinal layer attracted food, the oblique layer held it, and the transverse layer expelled it.[5]

A keen student of Latin, with an interest in medical history, could undoubtedly find many interesting points about the stomach and esophagus in the text of the *Fabrica.* Leibowitz,[3] for example, has presented a very convincing hypothesis concerning the possibility that Vesalius suffered from peptic ulcer. The basis of his argument is taken from a passage of the *Fabrica* wherein Vesalius complains of what appears to be hunger pains. Vesalius attributed the pain to a reflux of bile in "persons with a bilious disposition" from the duodenum into the stomach when the latter was empty.

An excellent means of appreciating Vesalius' description of the esophagus and stomach is afforded by Lind's translation[4] of the *Epitome,* a "remarkable condensation of the larger book," that is, the *Fabrica.* In Chapter III, "Concerning the Organs Which Minister to Nutrition by Food and Drink," the following is to be found:

> Food, as well as drink passes from the mouth to the stomach as into a storehouse along a path called the esophagus or gullet. This is extended by two special tunics appropriately formed to descend from the fauces behind the rough artery (trachea) and then along the vertebrae of the thorax through the transverse septum to the upper, or left-hand, orifice of the stomach.
>
> The stomach lies between the liver and the spleen under the septum. It is particularly roomy and rather long transversely, larger on the left-hand region of the body than on the right; it is equipped with two tunics suitable for distending and contracting and enclosed by a third covering derived from the peritoneum. The stomach is intertwined with many veins, arteries, and nerves. It concocts what is sent down to it from the mouth and changes this by an innate force into a thick milky juice. This passes through the lower orifice of the stomach from the higher region of its right side and is sent into the intestines.

Ansling's annotations to Lind's translation indicate that the "path" referred to in the text is the lumen and the two tunics are meant to be the mucosa and muscularis-adventitia.

Singer[6] has pointed out that Vesalius' treatment of the abdominal viscera was "passed over more cursorily than might have been expected, but in

many points the brief description is excellent." Singer specifically includes the stomach among the organs which were inadequately described. This latter view is perhaps too harsh. After Vesalius, the stomach could no longer be thought of as it formerly was, that is, a simple sphere receiving the hypothetical splenic duct for the evacuation of black bile from the spleen. Though the latter concept was to persist for many generations, the first step toward the true understanding of the structure and function of these organs had been taken.

Thus did Vesalius set the stage for the accumulation of our present body of knowledge of the stomach and esophagus. It is this basic information which was required before diseased states could be understood and rational therapy formulated.

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